



ÓRGANO DE DIFUSIÓN  
CIENTÍFICA DE LA  
ACADEMIA MEXICANA  
DE CIRUGÍA

FUNDADA EN 1933



PERMAYER MÉXICO  
www.permayer.com



ISSN: 2444-0507

# CIRUGÍA Y CIRUJANOS

## Content

### Original articles

**549 Clinical evolution of patients with infection associated with orthopedic devices in treatment with continuous negative pressure**

Jorge Quiroz-Williams, José R. Viveros-Encarnación, Suemmy Gaytán-Fernández, Rodolfo G. Barragán-Hervella, Carlos R. Rueda-Alvarado, América Ramírez-Polanco, M. Paloma Martínez-Senda, and Andrea M. Palma-Jaimes

**556 Role of contrast agent in evaluation of periprosthetic invasion in prostate cancer**

Hüseyin A. Kızıloğlu, Murat Beyhan, Erkan Gökçe, Yaşar Birişik, Çiğdem S. Salbaş, and Mustafa Yeşilyurt

**563 Beneficial effects of IVIG treatment on experimental-induced osteoporosis**

Savaş Özdemir and Oytun Erbas

**570 Effect of laparoscopic gastric sleeve vs. laparoscopic gastric bypass in Roux-Y on long-term weight loss in obese mexican population**

David Lomeli-Reyes, Gonzalo M. Torres-Villalobos, José M. Correa-Rovelo, Alejandro Díaz Girón-Gidi, Amado J. Athié-Athié, and Perla X. López-Almanza

**576 Finite element analysis evaluation of hypothetical alternative treatment scenarios for neglected developmental dysplasia of the hip**

Victor M. Araujo-Monsalvo, Marcos Martínez-Cruz, Lázaro Morales-Acosta, Víctor M. Domínguez-Hernández, Ramiro Cuevas-Olivo, Jesus A. Carrillo-Pelaes, Javier Perez-Orive, and Elisa Martinez-Coria

**582 Table of life for beneficiaries of the Institute of Security and Social Services of State Workers (ISSSTE), Mexico 2021**

Judith E. García-de-Alba-Verduzco, Javier E. García-de-Alba-Verduzco, Ramiro López-Elizalde, and Javier E. García-de-Alba-García

**590 Association of Vitamin D and magnesium levels with severity and mortality in patients with COVID-19**

Mariela M. García-Zendejas, Edgar A. Cano-Torres, and Luis E. Simental-Mendía

**595 Modified extensile calcaneal exposure is safe**

Chuansheng Fu, Baofu Wei, Hongjian Pei, Cunyin Xue, Jijuan Zhou, and Guodong Zhong

**605 Evaluation of hemostatic efficacy and safety of oxidized regenerated cellulose (Pahacel®) in coronary bypass surgery**

Hasan A. Keskin

**613 Acute kidney injury and mortality in patients with critical COVID-19 in Mexico: case-control study**

Ivette Mata-Maqueda, Juan C. Solís-Sáinz, Guadalupe Zaldivar-Lelo de Larrea, Ernesto Deloya-Tomas, Jorge López-Fermin, Ma Guadalupe Olvera-Ramos, Gabriela Castillo-Gutiérrez, Jorge D. Carrión-Moya, and Orlando R. Pérez-Nieto

Volume 92, No. 5, September-October 2024

Journal Citation Reports™ from Clarivate, 2022, Medline/PubMed, EBSCO Essentials™

# Clinical evolution of patients with infection associated with orthopedic devices in treatment with continuous negative pressure

## *Evolución clínica de los pacientes con infección asociada a dispositivos ortopédicos en tratamiento con presión negativa continua*

Jorge Quiroz-Williams<sup>1</sup>, José R. Viveros-Encarnación<sup>1</sup>, Suemmy Gaytán-Fernández<sup>1</sup>, Rodolfo G. Barragán-Hervella<sup>1\*</sup>, Carlos R. Rueda-Alvarado<sup>1</sup>, América Ramírez-Polanco<sup>1</sup>, M. Paloma Martínez-Senda<sup>2</sup>, and Andrea M. Palma-Jaimes<sup>2</sup>

<sup>1</sup>Unidad Médica de Alta Especialidad, Hospital de Traumatología y Ortopedia Manuel Ávila Camacho, Instituto Mexicano del Seguro Social;

<sup>2</sup>Facultad de Medicina, Universidad Popular Autónoma del Estado de Puebla. Puebla, Puebla, Mexico

### Abstract

**Objective:** To describe the use of negative pressure therapy with (TPNi) and without instillation (TPNs) as adjuvant treatment in the management of orthopedic device-associated infections (IADO). **Method:** Analytic observational study of records of patients with IADO managed with TPNi and TPNs with 0.9% saline solution, in patients > 18 years, operated on in 2018-2021. Clinical characteristics of infection, infectious agent as well as sociodemographic variables were evaluated. TPN was performed with the V.A.C. VERAFLOR<sup>TM</sup> system. Analysis with chi-square, Fisher and t-Student. Statistically accepted value  $p < 0.05$ . **Results:** Sample 40 patients. 75% male. Fractures 42.5% exposed and 57.5% closed. 92.5% applied prophylactic antibiotic (30-120 min). 35% plate implants, 12.5% centromedullary nail, 10% knee prosthesis and 12.5% hip. 47.5% bleeding < 500 mL. 72.5% surgical time of 2-4 hours. Previous hospitalization time, TPNs 3 weeks 55.9% and 4 weeks 26.5%; TPNi, 3 weeks 50% and 4 weeks 33.3%. Conservation of the implant 73.5% TPNs and 50% TPNi ( $p = 0.341$ ). Wound closure 91.2% with TPNs and 100% with TPNi ( $p = 1.000$ ). **Conclusions:** The use of TPNs and TPNi were useful as adjuvant treatments in the management of IADO, in addition they allowed to preserve the implant and wound closure in a large part of the patients.

**Keywords:** Orthopedic fixation devices. Prosthesis-related infections. Postoperative complications. Orthopedic equipment.

### Resumen

**Objetivo:** Describir el uso de la terapia de presión negativa con (TPNi) y sin instilación (TPNs) como tratamiento adyuvante en el manejo de infecciones asociadas a dispositivo ortopédico (IADO). **Método:** Estudio observacional analítico de expedientes de pacientes con IADO manejados con TPNi y TPNs con solución salina al 0.9%, mayores de 18 años, operados en el periodo 2018-2021. Se evaluaron las características clínicas de infección, el agente infeccioso y las variables sociodemográficas. La TPN se realizó con sistema V.A.C. VERAFLOR<sup>TM</sup>. Para los análisis se emplearon las pruebas  $\chi^2$ , Fisher y t de Student. Valor estadísticamente aceptado:  $p < 0.05$ . **Resultados:** La muestra fue de 40 pacientes, el 75% masculinos. Fracturas: 42.5% expuestas y 57.5% cerradas. En el 92.5% se aplicó antibiótico profiláctico (30-120 min). Implantes: 35% placas, 12.5% clavo centromedular, 10% prótesis de rodilla y 12.5% cadera. El 47.5% con sangrado < 500 mL. En el 72.5% un tiempo quirúrgico de 2-4 horas. Tiempo de hospitalización previa: TPNs 3 semanas 55.9% y 4 semanas 26.5%; TPNi 3 semanas 50% y 4

#### \*Correspondence:

Rodolfo G. Barragán-Hervella

E-mail: rodolfo68@icloud.com

2444-0507/© 2023 Academia Mexicana de Cirugía. Published by Permianer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Date of reception: 08-05-2023

Date of acceptance: 14-07-2023

DOI: 10.24875/CIRUE.M23000738

Cir Cir (Eng). 2024;92(5):549-555

Contents available at PubMed

[www.cirugiaycirujanos.com](http://www.cirugiaycirujanos.com)

semanas 33.3%. Conservación del implante: 73.5% TPNs y 50% TPNi ( $p = 0.341$ ). Cierre de herida: 91.2% con TPNs y 100% con TPNi ( $p = 1.000$ ). **Conclusiones:** El uso de TPNs y TPNi fue útil como tratamiento adyuvante en IADO, y además permitieron conservar el implante y el cierre de la herida en la mayoría de los pacientes.

**Palabras clave:** Fijación interna. Infecciones periprotésicas. Complicaciones posquirúrgicas. Implantes ortopédicos.

## Introduction

Health care-associated infections are considered a public health problem, both in developed and developing countries. Surgical site infections, including those associated with orthopedic devices (IADO)<sup>1,2</sup>, are classified as Health care-associated infections. IADOs are rare, but when they occur, they are serious, with a slow progression and cause prolonged disability, high Health care costs, and loss of well-being. IADOs can have various causes, but the primary one is contamination during the surgical procedure<sup>3-7</sup>. It also depends on the damage caused to the soft tissues, especially in traumatic orthopedic surgical procedures<sup>5,8,9</sup>.

The incidence of IADOs varies from country to country, as well as depending on the surgical procedure performed. Argüelles Martínez et al.<sup>4</sup> found in their study that the most frequent periprosthetic infection was that of the knee. Carvajal and Londoño<sup>10</sup> found that surgical site infections secondary to orthopedic implants had higher frequencies in surgical procedures involving the patella, tibia, and fibula, but were lower in forearm surgical procedures and joint replacements.

In general, the treatment of IADOs consists of cleaning and aggressive debridement. For over 30 years, subatmospheric pressure therapy has been used as an adjunct in the treatment of wound infections, as well as deep infections<sup>8,11-14</sup>. Negative pressure therapy (NPT) has two modalities: with permanent or intermittent pressure<sup>14,15</sup>.

NPT is not the panacea for treating both deep and superficial wound infections. Its success depends on the follow-up and care of the infection, the duration of use, and its combined management with aggressive surgical treatment involving serial washes and antibiotic therapy<sup>12,16,17</sup>.

The success in treating surgical site infections in orthopedic surgery is observed in cases involving osteosynthesis material or joint replacement. With the introduction of NPT, several studies show its success, as over 43% of cases preserve the implant, and infection eradication reaches 76-83% when combined with permanent instillation<sup>18,19</sup>.

Due to the fact that the use of NPT with instillation (NPTi) with antiseptic results in shorter treatment times than patients who are only managed with surgical washing and systemic antibiotics, reducing both costs and resources, the objective of this study was to describe the use of NPT with and without instillation as an adjunctive treatment in the management of infections associated with orthopedic implants, as well as to describe the hospital's experience with this therapy, the clinical evolution, and the microbiological characterization of patients with this type of infection.

## Method

An analytical, observational, cross-sectional, and retrospective study was conducted on patients with IADO who were treated with either NPTi or NPT without instillation (NPTw) with saline solution. Prior to its implementation, this study was reviewed and approved by the health research and ethics committees, with the registration number R-2019-2105-046.

The sampling technique was non-probabilistic, at the researcher's discretion, but a sample size calculation was not performed as all patients who met the inclusion criteria from January 2018 to May 2021 were considered. Patients over 18 years of age with surgical wound infections who received NPT as an adjunct to treat IADO, without distinction of sex, and who had a complete clinical file were included. Patients with incomplete clinical records and those who did not receive NPT as an adjunctive treatment were excluded. Patients who abandoned NPT before the clinical condition was healed or those who did not receive NPT properly were eliminated.

Data were collected from the hospital's clinical services database, identifying those who presented surgical wound infections. Variables collected from the clinical records included age, sex, comorbidities, smoking, and body mass index (BMI), as well as clinical signs (fever, fistula, induration, and redness of the wound) and laboratory values indicative of infection (leukocyte count, hemoglobin, hematocrit, C-reactive protein [CRP], sedimentation rate, and proteins), previous management history (open fractures, implant

placement, prophylactic antibiotics during the initial surgery, transoperative bleeding, and type of procedure), initial surgery time, infection evolution time, and bacteriological data (etiologic agent, antibiotic resistance, and antibiotic sensitivity). Open fractures were categorized according to the Gustillo-Anderson classification.

The decision to apply NPTi was at the surgeon's discretion. Surgical procedures were performed by senior medical professionals with experience in managing bone infections, and they had prior training in negative pressure system placement.

Before applying the NPT, all patients underwent aggressive surgical debridement, predominantly aiming to conserve the implant as long as no loosening was observed. Once the wound bed was prepared, an open-cell reticulated polyurethane foam sponge (V.A.C.® GranuFoam™) was placed. For wound closure, an acrylic adhesive cover was used, which connected to the suction tube of the V.A.C. VERAFLOR™ system. Instillation was performed with 0.9% saline solution, with an instillation time of 3 hours, 30 minutes of suction, and 15 minutes of retention. The suction pressure was set at a continuous pressure of 125 mmHg.

NPT was changed every 7 days, with sponge and container replacement. Each sponge change included taking a culture from the wound bed. The criterion for discontinuing NPT was having two negative cultures, with granulation tissue present and no purulent exudate.

In the statistical analysis, qualitative variables were expressed as frequencies and percentages, while numerical variables were expressed as mean and standard deviation (SD). For inferential analysis, the chi-square test was used for associations between polytomous variables, and Fisher's exact test was used for dichotomous variables. For associations between quantitative variables, the Student's t-test was applied. A p-value of < 0.05 was considered statistically significant.

## Results

During the study period, 2033 patients presented fractures, and hip or knee joint replacement was performed on 1503 patients, of which only 60 were identified with orthopedic implant-associated infections (IADO) who used negative pressure therapy (NPT) as an adjunct treatment. However, 20 had to be excluded because NPT was not applied properly, leaving a sample of 40 patients. Of the final sample, 75% were

**Table 1. Sociodemographic Variables (n = 40)**

Variables	n (%)
Sex	
Male	30 (75)
Female	10 (25)
Weight	
Underweight	5 (12.5)
Normal weight	12 (30)
Overweight	20 (50)
Obesity grade I	3 (7.5)
Comorbidity	
Diabetes mellitus	12 (30)
Systemic arterial hypertension	6 (15)
None	22 (55)

**Table 2. Orthopedic Diagnoses (n = 40)**

Diagnoses	n (%)
Open fracture	
IIIA	4 (10)
IIIB	9 (22.5)
IIIC	4 (10)
Closed fracture	23 (57.5)
Osteoarthritis	
Gonarthrosis	2 (5)
Coxarthrosis	4 (10)

male. The mean age was 43.2 years (SD, 16.8; range: 19-76). A total of 55% had no comorbidities. 50% were overweight, 30% had normal weight, and 12.5% were underweight (Table 1); the mean BMI was 25 (SD, 0.8; range: 10-40). Among the orthopedic diagnoses, 42.5% of the sample had an open fracture (Gustilo and Anderson), and 57.5% had a closed fracture. 11.8% had chronic degenerative conditions (Table 2).

When describing the surgical management history of the patients who developed IADO, regarding the surgical risk according to the ASA (American Society of Anesthesiologists) classification, it was found that 92.5% were ASA II, and 17.5% were ASA III. The prophylactic antibiotic administration time was 30 to 120 minutes before surgery in 92.5%. The most widely administered antibiotic was cephalexin (52.5%). The most widely used orthopedic implants were plates (35%), intramedullary nails (12.5%), and minimal osteosynthesis (12.5%). Surgical bleeding of < 500 mL was reported in 47.5%, and > 500 mL in 50%. The surgical time was < 2 hours in 25%, 2-4 hours in 72.5%, and > 4 hours in 2.5% (Table 3).



**Table 3. Surgical History in Patients with Infections Associated with Orthopedic Devices (n = 40)**

Antecedents	n (%)
Surgical risk	
ASA II	33 (82.5)
ASA III	7 (17.5)
Antibiotic prophylaxis time	
30-120 min	37 (92.5)
> 120 min	3 (7.5)
Prophylactic antibiotic	
Cefalexin	21 (52.5)
Cefalotin	9 (22.5)
Ceftriaxone	10 (25)
Orthopedic implant	
Plate	14 (35)
Centromedullary nail	5 (12.5)
Minimal osteosynthesis	5 (12.5)
Knee prosthesis	4 (10)
Hip prosthesis	5 (12.5)
Pedicule screws	2 (5)
Surgical bleeding	
< 500 mL	19 (47.5)
500-999 mL	20 (50)
1000-1400 mL	1 (2.5)
Surgical time	
< 2 hours	10 (25)
2-4 hours	29 (72.5)
> 4 hours	1 (2.5)

Regarding the clinical signs of patients with IADO, induration (17.5%), redness (95%), fistula (25%), and fever (42.5%) were observed. The time to onset of infection was < 3 months in 72.5%, 3-24 months in 17.5%, and > 24 months in 10% (Table 4).

Among the initial laboratory values, CRP levels were 5-10 mg/dL in 35%, 11-20 mg/dL in 60%, and 21-50 mg/dL in 5%. Total protein levels were altered in 57.5% of the patients (Table 4).

Initial radiographs showed segment-bone interface in 7.5% and osteolysis in 12.5% (Table 4).

Regarding the hospitalization time before NPT use and its type, for NPT without instillation (NPTw), it was 1 week in 2.9%, 2 weeks in 5.9%, 3 weeks in 14.7%, 4 weeks in 41.2%, 5 weeks in 20.6%, 6 weeks in 8.8%, and 7 weeks in 5.9%; for NPT with instillation (NPTi), it was 4 weeks in 50%, 5 weeks in 33.3%, and 6 weeks in 16.7% ( $p = 0.864$ ) (Table 5).

Regarding the type of NPT used, 85% used NPTw, and 15% used NPTi. Regarding the usage time, for NPTw, 14.7% used it for 2 weeks, 55.9% for 3 weeks, 26.5% for 4 weeks, and 2.9% for 5 weeks; for NPTi, 16.7% used it for 2 weeks, and 50% for 3 weeks.

**Table 4. Clinical Signs, Laboratory Values, and Initial Radiological Findings in Patients with Infections Associated with Orthopedic Devices (n = 40)**

Variables	n (%)
Time of onset of infection	
< 3 months	29 (72.5)
3-24 months	7 (17.5)
> 24 months	4 (10)
Induration	
Yes	33 (82.5)
No	7 (17.5)
Temperature	
< 37°C	14 (35)
37-37.9°C	9 (22.5)
38-38.5°C	16 (40)
> 38.5°C	1 (2.5)
Redness	
Yes	38 (95)
No	2 (5)
Fistula	
Yes	10 (25)
No	30 (75)
Radiographs	
No radiographic signs	32 (80)
Segment-bone interface	3 (7.5)
Osteolysis	5 (12.5)
C-reactive protein	
5-10 mg/dL	14 (35)
11-20 mg/dL	24 (60)
21-50 mg/dL	2 (5)
Total proteins	
Altered	23 (57.5)
No alteration	17 (42.5)

Regarding the type of NPT used, 85% received NPTw, and 15% received NPTi. Regarding the duration of use, for NPTw, 14.7% used it for 2 weeks, 55.9% for 3 weeks, 26.5% for 4 weeks, and 2.9% for 5 weeks; for NPTi, 16.7% used it for 2 weeks, 50% for 3 weeks, and 33.3% for 4 weeks. Implant preservation was observed in 73.5% of patients with NPTw and 50% with NPTi, while the implant had to be removed in 26.5% of patients with NPTw and 50% with NPTi ( $p = 0.341$ ). Wound closure was performed in 91.2% of patients with NPTw and 100% with NPTi ( $p = 1.000$ ) (Table 5).

When associating initial and final laboratory values with the type of NPT, with NPTw, the initial hemoglobin had a mean of  $11.35 \pm 3.4$  mg/dl and with NPTi,  $9.2 \pm 1.9$  mg/dl ( $p = 0.042$ ). The final hemoglobin had a mean of  $13.1 \pm 1.4$  mg/dl with NPTw and  $12.3 \pm 1.5$  mg/dl with NPTi ( $p = 0.251$ ). The initial leukocyte count was

**Table 5. Association of Negative Pressure Therapy Type with Duration of Use, Implant Preservation, Wound Closure, and Hospitalization Time (n = 40)**

Variables	NPTw (n = 34) n (%)	NPTi (n = 6) n (%)	Total n (%)	Significance*
Duration of use				
2 weeks	5 (14.7)	1 (16.7)	6 (15)	0.958
3 weeks	19 (55.9)	3 (50)	22 (55)	
4 weeks	9 (26.5)	2 (33.3)	11 (27.5)	
5 weeks	1 (2.9)	0	1 (2.5)	
Preservation of orthopedic implant				
Yes	25 (73.5)	3 (50)	28 (70)	0.341
No	9 (26.5)	3 (50)	12 (30)	
Wound closure				
Yes	31 (91.2)	6 (100)	37 (92.5)	1.000
No	3 (8.8)	0	3 (7.5)	
Previous hospitalization time				
1 week	1 (2.9)	0	1 (2.5)	0.864
2 weeks	2 (5.9)	2 (33.3)	4 (10)	
3 weeks	5 (14.7)	1 (16.7)	6 (15)	
4 weeks	14 (41.2)	0	14 (35)	
5 weeks	7 (20.6)	1 (2.5)	8 (20)	
6 weeks	3 (8.8)	2 (5)	5 (12.5)	
7 weeks	2 (5.9)	1 (12.5)	3 (7.5)	

\*Significance:  $p < 0.05$ .

NPTi: Negative Pressure Therapy with Instillation; NPTw: Negative Pressure Therapy without Instillation.

13,097  $\pm$  4641.7 per field with NPTw and 13,133.3  $\pm$  4195.6 per field with NPTi ( $p = 0.985$ ), and the final count was 7,758.8  $\pm$  1578.6 per field with NPTw and 7,966.7  $\pm$  242.2 per field with NPTi ( $p = 0.475$ ). The initial C-reactive protein (CRP) was 2.7  $\pm$  0.6 with NPTw and 2.7  $\pm$  0.5 with NPTi, and the final CRP was 1.1  $\pm$  0.4 with NPTw and 1.2  $\pm$  0.4 with NPTi ( $p = 0.915$ ). The initial total proteins were 5.9  $\pm$  0.9 with NPTw and 6.3  $\pm$  1.0 with NPTi ( $p = 0.366$ ), and the final total proteins were 6.5  $\pm$  0.7 with NPTw and 6.2  $\pm$  0.4 with NPTi ( $p = 0.258$ ) (Table 6).

## Discussion

IADO present a significant challenge for orthopedic surgeons; the costs associated with their treatment are six to seven times higher compared to non-infected procedures<sup>20</sup>. In this study, it was observed that the use of Negative Pressure Therapy (NPT) in IADO allows for the preservation of the orthopedic implant in a large percentage of patients. Most authors who have used NPT for treating IADO report that in a large percentage (75-85%) of cases, the orthopedic implant is retained<sup>16,17,21,22</sup>. In contrast to the literature, the percentage of implant preservation in this study was similar to what has been reported, but only with NPTw (73.5%), while among patients treated with NPTi, only half preserved the implant, but without statistical

significance, possibly due to group heterogeneity. Webb<sup>23</sup> argues that the use of NPTi shows favorable results, but studies of higher quality are needed to guarantee the efficacy of this therapy. West et al.<sup>24</sup> note that instillation may help eradicate infections in surgical sites with a high risk of infection, facilitating implant preservation, but could cause long-term tissue damage due to the toxicity of the instillation solution used. In this study, instillation was performed only with saline solution to avoid toxicity in surrounding tissues.

The use of NPTw and NPTi should be considered as an adjunctive treatment, for limited periods, and in carefully selected patients<sup>11,12</sup>. In this study, NPT was applied to patients who exhibited persistent IADO after initial treatment and who showed no clinical improvement. The length of hospitalization varied depending on associated factors. It is important to note that the population to which both NPTw and NPTi were applied had, to a large extent, hospitalizations of more than 4 weeks before the application of NPT. These types of therapies have shown their effectiveness in managing deep infections<sup>13</sup>. Falci et al.<sup>25</sup> identify potential variables for surgical wound contamination as the clinical condition of patients (ASA), the type of surgical procedure, and the duration of the surgery. Ángeles-Garay et al.<sup>9</sup> report risk factors for developing surgical site infections, including smoking history, low weight,

**Table 6. Initial and Final Laboratory Values of Patients with Orthopedic Device-Associated Infections Treated with Negative Pressure Therapy (n = 40)**

Parameters	NPTw (Mean $\pm$ SD)	NPTi (Mean $\pm$ SD)	Significance*
Initial Hemoglobin	11.35 $\pm$ 3.4	9.2 $\pm$ 1.9	0.042
Final Hemoglobin	13.1 $\pm$ 1.4	12.3 $\pm$ 1.5	0.251
Initial Leukocytes	13,097.1 $\pm$ 4641.7	13,133.3 $\pm$ 4195.6	0.985
Final Leukocytes	7,758.8 $\pm$ 1578.6	7,966.7 $\pm$ 242.2	0.475
Initial C-reactive Protein	2.7 $\pm$ 0.6	2.7 $\pm$ 0.5	0.871
Final C-reactive Protein	1.1 $\pm$ 0.4	1.2 $\pm$ 0.4	0.915
Initial Total Proteins	5.9 $\pm$ 0.9	6.3 $\pm$ 1.0	0.366
Final Total Proteins	6.5 $\pm$ 0.7	6.2 $\pm$ 0.4	0.258

\*Significance:  $p < 0.05$ .

NPTi: Negative Pressure Therapy with Instillation; NPTw: Negative Pressure Therapy without Instillation.

inadequate handwashing techniques, blood transfusions during surgery, contaminated surgeries, hospital stays of 8 to 14 days, and the presence of venous catheters and urinary catheters for 1 to 3 days. This study did not aim to identify risk factors for the development of IADO, but as comorbidities, half of the patients studied had diabetes mellitus or systemic hypertension, and most patients had normal weight or overweight, with only small percentages having obesity or underweight. More than half of the patients presented a closed fracture, with a smaller proportion having an exposed fracture (Gustillo-Anderson III). Regarding surgical risk, 82.5% of the patients were ASA II. The surgical time in the primary surgery was between 2 and 4 hours for 72.5%, and in more than half of the cases, the surgical bleeding was less than 1000 mL.

Regarding laboratory values after NPT and NPTi application, a significant reduction was observed in the leukocyte count ( $p = 0.475$ ), CRP ( $p = 0.915$ ), and total proteins ( $p = 0.258$ ).

Izadpanah et al.<sup>17</sup> establish that factors contributing to NPT failure in patients with postoperative infections after osteosynthesis include late infection manifestations ( $> 4$  weeks), bacterial mixture, significant soft tissue injury, and high CRP values ( $> 20$  mg/L). This study only showed laboratory values at the end of the NPT treatment, where a decrease in CRP was observed, but it was not statistically significant, possibly due to the small sample size.

The strength of this study lies in comparing 2 NPT techniques, and it also demonstrated the effectiveness of these therapies as adjuncts in the treatment of IADO, allowing implant preservation in a large percentage of patients. The weaknesses of the study include the

heterogeneity between the groups and the small number of patients, which is why the statistical values were not significant. Furthermore, patients were not followed up, but this will be addressed in future studies, along with a cost study involving a larger number of patients, with a 12-month follow-up. It is also important to note that this therapy was administered after surgical debridement and antibiotic therapy, so a comparison of hospital stay reduction times was not made, suggesting the use of NPT from the beginning for IADO management without comparing it to patients managed without NPT.

## Conclusions

The use of NPTw and NPTi was useful as an adjunct treatment in the management of IADO and also allowed for the preservation of the orthopedic implant and definitive closure of the surgical wound in a large portion of the patients. In this study, there was no significant difference in the outcomes when comparing both NPT techniques. The choice between NPTw and NPTi is left to the discretion of the surgeon. More randomized clinical trials with a larger number of patients and longer follow-up are required, as well as applying NPT at the start of treatment to demonstrate its effectiveness in eradicating IADO and determine which NPT technique is best.

## Acknowledgments

The authors would like to thank the clinical services of the Extremities and Spine and Hip Unit at the Manuel Ávila Camacho Traumatology and Orthopedic Specialty Hospital for their support.

## Funding

None declared.

## Conflicts of interest

None declared.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that no patient data appear in this article.

**Right to privacy and informed consent.** The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

## References

- Berriós-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, et al. Centers for disease control and prevention guideline for the prevention of surgical site infection. *JAMA Surg.* 2017;152:784-91.
- Ducel G, Fabry J, Nicolle L, Girard R, Perraud M, Prüss A, et al. Guía práctica. Prevención de las infecciones nosocomiales. WHO/CDS/CSR/EPH; 2009.
- Instituto Mexicano del Seguro Social. Diagnóstico y tratamiento de las infecciones asociadas a dispositivos ortopédicos, prótesis y/o material de osteosíntesis. 2013. Disponible en: <http://www.imss.gob.mx/profesionales/guiasclinicas/Pages/guias.aspx>.
- Argüelles-Martínez O, Rivera-Villa A, Miguel-Pérez A, Torres-González R, Pérez-Atanacio JM, Mata-Huerta A, et al. Agentes etiológicos más frecuentes en infecciones periprotésicas de artroplastia primaria de rodilla y cadera en adultos mayores. *Acta Ortop Mex.* 2016;30:116-8.
- García-Aldeco M, Martínez-Hernández A, González-Gámez M. Infección asociada a implantes ortopédicos. *Lux Médica.* 2019;41:59-66.
- Suárez-Ahedo C, Obil-Chavarría C, Gil-Orbezo F, García-Félix Díaz G. Prevención de infecciones en el perioperatorio de la artroplastia primaria de cadera y rodilla. *Acta Ortop Mex.* 2011;25:4-11.
- Muñoz-Mahamud E, García S, Bori G, Martínez-Pastor JC, Zumbado JA, Riba J, et al. Comparison of a low-pressure and a high-pressure pulsatile lavage during debridement for orthopaedic implant infection. *Arch Orthop Trauma Surg.* 2011;131:1233-8.
- Nam D, Sereshon RA, Levine BR, Della Valle CJ. The use of closed incision negative-pressure wound therapy in orthopaedic surgery. *J. Am Acad Orthop Surg.* 2018;26:295-302.
- Ángeles-Garay U, Morales-Márquez LI, Sandoval-Balanzarios MA, Velázquez-García JA, Méndez-Cano AF. Factores de riesgo relacionados con infección del sitio quirúrgico en cirugía electiva. *Cir Cir.* 2014;82:48-62.
- Carvajal R, Londoño A. Factores de riesgo e infección del sitio quirúrgico en procedimientos de cirugía ortopédica con prótesis. *Rev Chil Infectol.* 2012;29:395-400.
- Robert N. Negative pressure wound therapy in orthopaedic surgery. *Orthop Traumatol Surg Res.* 2017;103(1S):S99-103.
- Cid N, García Ruano F, Athenea Luanco Gracia A, Jiménez Martín M, Sicre González A. Terapia por presión negativa en el manejo de heridas complejas en traumatología. Innovación e indicación. *Rev S And Traum y Ort.* 2014;31:17-23.
- Aceves-Pérez A, Medina-Romero P, Ávila-Jiménez MJ. Terapia de presión negativa como alternativa en el manejo de la infección en cirugía de columna. *Columna.* 2013;12:330-3.
- Kurra S, Rashid A, Yirenkyi H, Castle P, Lavelle WF. Outcomes of negative pressure wound therapies in the management of spine surgical site wound infections. *Int J Spine Surg.* 2020;14:772-7.
- Kelm J, Schmitt E, Anagnostakos K. Vacuum-assisted closure in the treatment of early hip joint infections. *Int J Med Sci.* 2009;6:241-6.
- Lehner B, Fleischmann W, Becker R, Jukema GN. First experiences with negative pressure wound therapy and instillation in the treatment of infected orthopaedic implants: a clinical observational study. *Int Orthop.* 2011;35:1415-20.
- Izadpanah K, Hansen S, Six-Merker J, Helwig P, Südkamp NP, Schmal H. Factors influencing treatment success of negative pressure wound therapy in patients with postoperative infections after osteosynthetic fracture fixation. *BMC Musculoskelet Disord.* 2017;18:247.
- Beckmann NA, Hanslmeier MG, Omlor GW, Feisst M, Maier MW, Lehner B. Is negative pressure wound therapy with instillation suitable for the treatment of acute periprosthetic hip joint infection? *J Clin Med.* 2021;10:3246.
- Ene R, Panti Z, Albu E, Ene P, Cirstoiu MM, Cirstoiu FC. Negative pressure, a "solution" in the treatment of infected knee prosthesis? *Maedica (Bucur).* 2015;10:5-9.
- Depypere M, Kuehl R, Metsemakers WJ, Senneville E, McNally MA, Obremskey WT, et al. Recommendations for systemic antimicrobial therapy in fracture-related infection: a consensus from an international expert group. *J Orthop Trauma.* 2020;34:30-41.
- Chang CW, Chan HZ, Lim SW, Khoo E, Zulkiflee O. Negative pressure wound therapy in infected wound following posterior spinal instrumentation using simple self-assembled system: a case report. *Malays Orthop J.* 2014;8:49-51.
- Pelham FR, Kubiak EN, Sathappan SS, Di Cesare PE. Topical negative pressure in the treatment of infected wounds with exposed orthopaedic implants. *J Wound Care.* 2006;15:111-6.
- Webb LX. The impact of negative pressure wound therapy on orthopaedic infection. *Orthop Clin North Am.* 2017;48:167-79.
- West JM, Jordan SW, Mendel E, Khan SN, Chandawarkar RY, Valerio IL. Instillation negative pressure wound therapy: an effective tool for complex spine wounds. *Adv Wound Care (New Rochelle).* 2018;7:333-8.
- Falci Ercole F, Castro Franco LM, Rezende Macieira TG, Crespo Wenceslau LC, Nascimento de Resende HI, Machado Chianca TC. Riesgo para infección de sitio quirúrgico en pacientes sometidos a cirugías ortopédicas. *Rev Latino-Am Enfermagem.* 2011;19:1-8.

# Role of contrast agent in evaluation of periprostatic invasion in prostate cancer

## *Papel del agente de contraste en la evaluación de la invasión periprostática en el cáncer de próstata*

Hüseyin A. Kızıloğlu<sup>1\*</sup>, Murat Beyhan<sup>1</sup>, Erkan Gökçe<sup>1</sup>, Yaşar Birişik<sup>1</sup>, Çiğdem S. Salbaş<sup>2</sup>, and Mustafa Yeşilyurt<sup>3</sup>

<sup>1</sup>Department of Radiology, Tokat Gaziosmanpaşa University Faculty of Medicine, Tokat; <sup>2</sup>Department of Radiology, Bandırma Training and Research Hospital, Balıkesir; <sup>3</sup>Department of Radiology, Erzurum Training and Research Hospital, Erzurum. Türkiye

### Abstract

**Objective:** Our study aims to demonstrate the detection of invasion by biparametric prostate MRI (bpMRI). **Materials and methods:** The cases whose histopathological diagnosis was prostate cancer (PCa) and whose mpMRI report was reported as PIRADS 4 and 5 were evaluated retrospectively by two radiologists with different prostate imaging experiences. The images were grouped into two data sets. Dataset-1 was bpMRI, and dataset-2 was mpMRI. Two radiologists first evaluated dataset-1 independently of each other, and 1 month later, dataset-2. They recorded whether there was an invasion and where it was seen in the patients. Then, the results were compared. **Results:** A total of 75 patients were included in the study. Periprostatic invasion was detected in 33 of the patients. Both the 1<sup>st</sup> reader and the 2<sup>nd</sup> reader image detected all the cases with invasion (100%) separately between dataset-1 and set-2. Compatibility for image dataset-1 and dataset-2 between both readers was observed to be excellent. **Conclusions:** There is no need to use contrast agent to evaluate periprostatic invasion and to have an idea about local staging in PCa patients.

**Keywords:** Periprostatic invasion. Contrast agent. Prostate. Multiparametric. Biparametric.

### Resumen

**Objetivo:** Nuestro estudio tiene como objetivo demostrar la detección de la invasión por resonancia magnética biparamétrica de próstata (BPMRI). **Material y métodos:** Los casos cuyo diagnóstico histopatológico fue PCA y cuyo informe MPMRI se informó como Pirads 4 y 5 fueron evaluados retrospectivamente por dos radiólogos con diferentes experiencias de imágenes de próstata. Las imágenes se agruparon en dos conjuntos de datos. DataSet-1 fue BPMRI, DataSet-2 fue MPMRI. Dos radiólogos evaluaron por primera vez el conjunto de datos 1 independientemente el uno del otro, y 1 mes después, el conjunto de datos-2. Registraron si había una invasión y dónde se vio en los pacientes. Luego se compararon los resultados. **Resultados:** Se incluyeron un total de 75 pacientes en el estudio. La invasión periprostática se detectó en 33 de los pacientes. Tanto el primer lector como la imagen del segundo lector detectaron todos los casos con invasión (100%) por separado entre el conjunto de datos-1 y el set-2. Se observó que la compatibilidad para el conjunto de datos de imágenes-1 y el conjunto de datos entre ambos lectores era excelente. **Conclusiones:** No es necesario usar el agente de contraste para evaluar la invasión periprostática y tener una idea sobre la puesta en escena local en pacientes con PCA.

**Palabras clave:** Invasión periprostática. Agente de contraste. Próstata. Multiparamétrico. Biparamétrico.

#### \*Correspondence:

Hüseyin A. Kızıloğlu

E-mail: alperkizloglu@hotmail.com

2444-0507/© 2023 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Date of reception: 10-03-2023

Date of acceptance: 15-09-2023

DOI: 10.24875/CIRUE.M23000739

Cir Cir (Eng). 2024;92(5):556-562

Contents available at PubMed

[www.cirugiaycirujanos.com](http://www.cirugiaycirujanos.com)



## Introduction

Prostate cancer (PCa) is one of the most diagnosed and leading causes of cancer-related death in men<sup>1,2</sup>. Prostate cancer is suspected in the presence of a positive digital rectal examination and/or elevated prostate-specific antigen (PSA). This antigen, which is widely used in PCa screening in the clinic, is secreted from both normal prostate epithelium and malignant cells<sup>2</sup>. Conventional radiological evaluations such as ultrasonography (US), computed tomography (CT), and contrast-enhanced lower abdomen magnetic resonance imaging (MRI) are insufficient in detecting and staging prostate cancer. Therefore, with the publication of Prostate Imaging Reporting Data System version 1 (PIRADS v1) in 2012, multiparametric prostate MRI (mpMRI) was brought into the literature and routine practice, and the reporting system was simplified with PIRADS v2 in 2015<sup>3</sup>. PIRADS v2.1 was published in 2019 by the PIRADS committee due to the feedback of the uncertainties and limitations of PIRADS v2 in many studies<sup>4</sup>. The use of mpMRI in the diagnosis of PCa has been increasing in recent years, and mpMRI is also used for treatment planning, local staging, determination of biopsy localization, and estimation of tumor aggressiveness<sup>5</sup>. According to the PIRADS guideline published by the European Society of Urogenital Radiology (ESUR) in 2012, the mpMRI protocol consists of multiplanar T1-weighted (T1W) and T2-weighted (T2W) images, diffusion-weighted images (DWI), and dynamic contrast-enhanced (DCE) sequences<sup>3</sup>. In local staging, which is an important step after the diagnosis of PCa, the specificity of MRI is high, but the specificity is low in demonstrating microscopic extraprostatic extension. The current method used to determine whether the tumor has exceeded the prostate border is PSA, Gleason score, positive core percentage, and digital rectal evaluation<sup>6</sup>. These data are combined with the patient's clinic to predict possible extraprostatic extension, seminal vesicle invasion, lymph node involvement, and distant metastasis. Prostate MRI directly visualizes the extraprostatic extension instead of these evaluations. Although MRI has relatively low sensitivity (38%) in demonstrating extraprostatic extension in early studies, it is highly specific<sup>7</sup>.

In PIRADS v2 published by ESUR, the level of contribution of DCE to diagnosis was reduced. In the differentiation of clinically significant PCa, DWI was used for the peripheral zone (PZ) and T2W images were

used as the dominant sequence for the transitional zone (TZ). It was also suggested that the contribution of DCE to the diagnosis in PCa is minimal for PZ lesions and is useless for TZ lesions<sup>8</sup>. According to PIRADS v2, DCE only elevates PZ lesions from the PIRADS-3 category to the PIRADS-4 category. In some studies, it is argued that DCE does not contribute significantly to the diagnosis of clinically significant PCa, and it is suggested that only T2-weighted images and DWI images are sufficient<sup>9-11</sup>. In this situation, the place of contrast series in diagnosing clinically significant PCa has become controversial. Accordingly, biparametric prostate MRI (bpMRI), in which only T2-weighted images and DWI images are considered, has been discussed. There are many studies in the literature comparing mpMRI and bpMRI in detecting clinically significant PCa<sup>12-14</sup>. However, bpMRI studies focusing on detecting extraprostatic invasion used in local staging are very limited in the literature.

The main purpose of this study is to demonstrate the diagnostic accuracy of bpMRI in detecting extraprostatic invasion, which is especially important in local staging. In addition, in this study, we aimed to show the agreement of two radiologists with different experiences in the evaluation of extraprostatic invasion with bpMRI.

## Materials and method

The study was carried out retrospectively and the study was started after the approval of the local ethics committee dated 28 July 2022 and numbered 22-KAEK-155. Our study was carried out according to the "Helsinki Declaration".

## Case selection

In our study, patients diagnosed with PCa histopathologically between January 2019 and June 2022 were examined. Inclusion criteria for the study were patients with elevated PSA and/or positive digital rectal examination findings, patients with mpMRI examination before and within 6 months of prostate biopsy, patients with mpMRI examination within 6 months before prostatectomy, mpMRI report PIRADS 4 and 5 according to PIRADS v2.1 reported patients. Apart from the two readers who performed the study, the PIRADS score was performed by a genitourinary system radiologist with 5 years of prostate MRI reading experience. Exclusion criteria were history of previous

surgery for the prostate, incomplete histopathological data, inadequate mpMRI image quality (artifactual image due to patient movement, presence of magnetic susceptibility artifact due to pelvic surgery such as total hip replacement, presence of artifact on DWI images due to full rectum and inability to comment on the presence of invasion due to collapsed seminal vesicles), and hormonal therapy before mpMRI.

### ***MRI protocol***

All patients underwent MRI examination on a 1.5 T device (SIGNA™ Explorer-60 cm GE Healthcare) without using an endorectal coil. MRI sequences used axial fast-spin echo T1W without fat suppression, axial, coronal, and sagittal turbo-spin echo T2W without fat suppression, axial single-shot spin echo-planar DWI images, and T1 Lava three-dimensional spoiled gradient echo pulse sequences without fat suppression. The technical parameters of the sequences are T1W; TR/TE 817/11; slice thickness 3 mm; no slice gap; matrix 256 × 256, and field of view (FOV) 200 × 200 mm for axial images. T2W; TR/TE 8590/108; slice thickness 3 mm; no slice gap; matrix 256 × 256 and FOV 200 × 200 mm for axial images. For DWI, TR/TE 7100/66, slice thickness 3 mm, no slice gap, matrix 256 × 256 and FOV 200 × 200 mm for axial images and b values are 0, 500, and 1500 s/mm<sup>2</sup>. The apparent diffusion coefficient map was calculated for each patient and T1 Lava; TR/TE 4/1, slice thickness 3 mm, no slice gap, matrix 256 × 256 and FOV 200 × 200 mm for axial images. Gadolinium-based contrast agents 0.1 mmol/kg were used for contrast images. Dynamic images were acquired with 30 phases every 7 s. The examination time for the patients lasted approximately 40–45 min.

Before the examination, the patients were advised to sexual abstinence for 3 days. During the examination, care was taken to ensure that the rectum of the patients was empty. Buscopan 20 mg/kg intravenous injection was administered to reduce intestinal peristalsis if there were no contraindications during the examination.

### ***Image analysis***

The images were evaluated by two radiologists (1<sup>st</sup> reader 5-year prostate MRI reading experience and 2<sup>nd</sup> reader 2-year prostate MRI reading experience) with different experiences on evaluating

prostate MRI. Images were evaluated from a 21.3 inch 3MP IPS Screen medical monitor through Sectra IDS 7 Picture Archiving and Communication Systems. The images were divided into two sets. It was classified as image set-1 bpMRI (T2W, T1W, and DWI sequences) and image set-2 mpMRI (T2W, T1W, DWI, and DCE sequences). While evaluating patients in the study, readers did not look at contrast-enhanced images for bpMRI. Contrast-enhanced images were eliminated in the computer environment, and readers only viewed bpMRI images of the same patients. First, image set-1 was evaluated by both readers. After 1 month, in the second session, evaluation of the same patients, the image set-2 was examined by both readers. Readers evaluated the images independently of each other. At the end of the evaluation, periprostatic invasion was recorded for each patient as present/absent. Invasion sites; it was localized as extraprostatic (extension beyond the prostatic capsule to the fat planes), seminal vesicle invasion, and bladder invasion. In addition, protrusions and irregularities in the prostate contour, obliteration of the rectoprostatic angle, tumor-capsule interface larger than 1 cm, and neurovascular bundle involvement, defined as invasion criteria according to PIRADS v.2.1, were also recorded in the extraprostatic extension. The presence of invasion for image set-1 was accepted in cases where an extraprostatic soft-tissue lesion extending to the seminal vesicle and bladder and causing restriction in diffusion was detected. For image set-2, the presence of invasion was accepted when extraprostatic, seminal vesicle, and a contrasting soft-tissue lesion extending to the bladder were detected. Then, the obtained data were compared in terms of the presence and localization of invasion between readers and between image sets.

### ***Statistical analysis***

The SPSS 24 statistical software package (IBM Corp., Armonk, NY, USA) was used for all data analysis. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean, deviation, and minimum-maximum. Normality of distributions was evaluated using the Kolmogorov–Smirnov and Shapiro–Wilk W tests. Independent samples *t*-test was used as our data showed a normal distribution. *p* < 0.05 was considered statistically significant. The Cohen's kappa test was used to determine the level of compatibility among readers. Kappa coefficient; If it is < 0, weak

agreement, 0-0.20 agreement insignificant, 0.21-0.4 low agreement, 0.41-0.6 medium agreement, 0.61-0.8 high agreement, and 0.81-1 was evaluated as a perfect agreement.

## Results

A total of 75 male patients were included in the study. The mean age of these patients was calculated as  $66.49 \pm 7.57$  (48-86 years). On mpMRI, 35 (46.7%) of the patients were reported as PIRADS 4 and 40 (53.3%) as PIRADS 5. The mean PSA of the patients was  $16.17 \pm 13.95$  ng/mL (3.58-66 ng/mL). The histopathological report of all patients was reported as adenocancer. The mean age of the patients reported as PIRADS 4 was  $65.46 \pm 8.69$  years and the mean PSA of these patients was  $9.05 \pm 5.89$  ng/mL. The mean age of the patients reported as PIRADS 5 was  $67.4 \pm 6.4$  years and the mean PSA of these patients was  $22.4 \pm 15.94$  ng/mL (Table 1). There was no statistically significant difference between PSA values and age for patients reported as PIRADS 4 and 5.

Periprosthetic invasion was detected in 33 (44%) of the patients. All of the patients with invasion were reported as PIRADS 5. The mean age of the patients with invasion was  $67.97 \pm 6.35$  years and the mean PSA of these patients was  $24.95 \pm 16.32$  ng/mL. The mean age of the patients without invasion was  $65.33 \pm 8.29$ , and the mean PSA of these patients was  $9.27 \pm 5.74$  ng/mL (Table 1). A statistically significant difference was found between PSA values for patients with and without invasion ( $p < 0.001$ ). The most common invasion was extraprostatic (extension beyond the prostatic capsule into the fat planes) in 14 patients (42.4%) (Figs. 1 and 2). Seminal vesicle invasion was detected in 13 patients (39.4%), both seminal vesicle and bladder invasion were detected in 3 patients (9.1%), and both seminal vesicle and extraprostatic invasion were detected in 3 patients (9.1%).

Both the 1<sup>st</sup> and 2<sup>nd</sup> reader image data set-1 (bpMRI) and set-2 (mpMRI) detected all the cases with invasion (100%) separately. The compatibility between both readers for image data set-1 and set-2 was observed to be excellent (Kappa value +1) (Table 2).

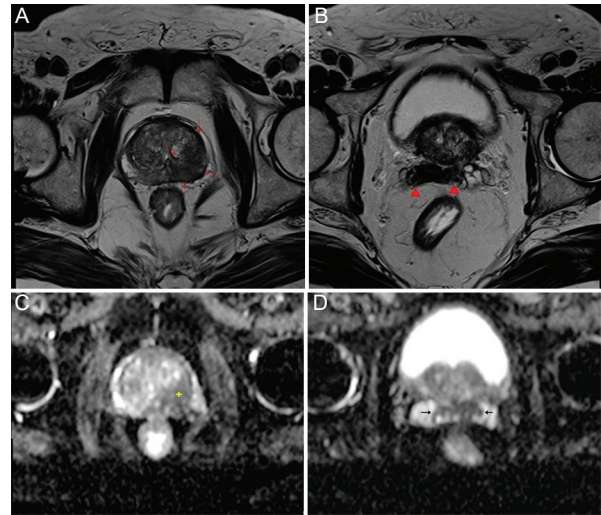
## Discussion

In our study, since all cases with invasion detected on mpMRI could be detected with bpMRI and excellent agreement was observed between two radiologists with different prostate imaging experiences in

**Table 1. Descriptive data of the patients**

Radiopathological data	Number/Percent	Age $\pm$ SD (year)	PSA $\pm$ SD (ng/mL)
PIRADS 4	35/46.7%	$65.46 \pm 8.69$	$9.05 \pm 5.89$
PIRADS 5	40/53.3%	$67.4 \pm 6.4$	$22.4 \pm 15.94$
Cases with invasion	33/44%	$67.97 \pm 6.35$	$24.95 \pm 16.32$
Cases with no invasion	42/56%	$65.33 \pm 8.29$	$9.27 \pm 5.74$
Total	75/100%	$66.49 \pm 7.57$	$16.17 \pm 13.95$

SD: standard deviation; PSA: prostate-specific antigen; PIRADS: prostate imaging reporting data system.

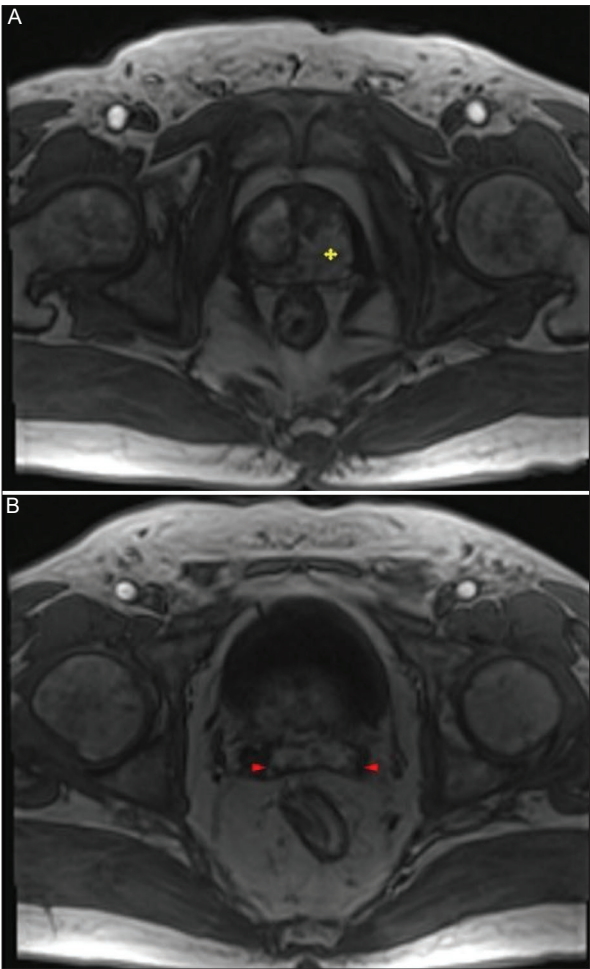


**Figure 1. A-D:** a 68-year-old male patient. PIRADS 5 lesion involving the anterior and posterior compartments of the middle peripheral zone on the left and involving the transitional zone anterior and posterior zone. The lesion extends to the base of the prostate in more superior sections and invades both seminal vesicles from there. **A:** T2-weighted image shows signal loss at the described location of the lesion (between the red arrows). **B:** T2-weighted image, it is observed that the lesion has invaded both seminal vesicles (red arrowheads). **C:** the apparent diffusion coefficient map, lesion appears hypointense (yellow mark). **D:** the apparent diffusion coefficient map shows that the lesion has invaded both seminal vesicles (between black arrows).

the detection of invasion on bpMRI, gross local staging of PCa could be performed by showing periprosthetic invasion by bpMRI.

With the change on prostate imaging over the years, the areas of use of contrast media are narrowing. Because, besides its minimal contribution to diagnostic accuracy, it has disadvantages that cannot be ignored. There are three major advantages to removing DCE from the protocol. These shorten the examination time, reducing the cost of the examination, and eliminating the possible undesirable effects of the contrast agent. Some known side effects linked to the use of gadolinium-based contrast agents include:





**Figure 2.** A and B: post-contrast T1-weighted image of the same patient without fat suppression. A: the lesion has heterogeneous contrast (yellow mark). B: seminal vesicle invasion is seen as a contrast-ing space-occupying formation (between the red arrowheads).

development of allergic reaction, systemic nephro-genic fibrosis and accumulation of contrast agent in the brain<sup>15</sup>. Other side effects are seen at a rate of 0.004-0.7% and include coldness or warmth at the injection site, pain at the injection site, nausea, vomit-ing, headache, paresthesia, and dizziness<sup>16</sup>. DCE is still included in clinical use and in the PIRADS v2.1 guideline. Because DCE has advantages such as de-tecting small PCa and following patients after radical prostatectomy<sup>11,17</sup>. In addition, the use of contrast agent has additional advantages such as increasing the diagnostic accuracy of some inexperienced radi-ologists and supporting the correct diagnosis if the image quality of DWI and/or T2W sequences is low<sup>16</sup>. However, it has also been shown that the use of DCE causes false positives in some benign conditions such as prostatitis and fibrosis<sup>18</sup>. The role of DCE in

**Table 2.** Compatibility among readers

Observers	Invasion detection (number/percent)		Kappa
	Data set-1 (bpMRI)	Data set-2 (mpMRI)	
Reader I	33/100%	33/100%	1
Reader II	33/100%	33/100%	

bpMRI: biparametric prostate magnetic resonance imaging; mpMRI: multiparametric prostate magnetic resonance imaging.

**Table 3.** bpMRI and mpMRI advantages

bpMRI (T2W, DWI) advantages	mpMRI (T2W, DWI, DCE) advantages
Examination time is short	Diagnostic accuracy increases if T2W and DWI image quality is poor
Possible side effects of the contrast agent are eliminated	Diagnostic accuracy increases in the presence of inexperienced radiologist
Cost is lower	Detection of small lesions becomes easier
Evaluation is easier	Contributes to diagnostic accuracy in uncertain cases

bpMRI: biparametric prostate magnetic resonance imaging; mpMRI: multiparametric prostate magnetic resonance imaging; T2W: T2 weighted; DWI: diffusion-weighted imaging; DCE: dynamic contrast enhanced.

diagnosis and staging is controversial. One advantage of using the bpMRI protocol is that it is easier to evalu-ate images than mpMRI. The comparison of mpMRI and bpMRI in terms of advantages is shown in table 3.

Studies on the use of bpMRI in local staging, which is the focus of our study, are limited. Although the specificity of prostate MRI is high in local staging, the sensitivity is low due to the inability of MRI to show microscopic extraprostatic extension<sup>4</sup>. In this instance, we think that imaging with DCE will not be of addi-tional benefit in showing the microscopic extension. Our results also detected periprostatic invasion at the same rate in contrast-enhanced and non-contrast se-ries, regardless of microscopic extension.

There are some studies showing that bpMRI has the same diagnostic accuracy as mpMRI in detecting clini-cally significant PCa according to PIRADS v2<sup>14,19-21</sup>. In a study that divided patients with suspected PCa into low-risk, intermediate-high-risk, and very high-risk pa-tients, it was reported that only bpMRI evaluation would be sufficient in the very high-risk patient group (having a very high PSA and positive digital rectal examination finding)<sup>22</sup>. According to this study, our patient group

falls into the very high-risk category, and we argue that bpMRI will be sufficient to evaluate patients in this category. Recent evidence has revealed that the bpMRI protocol may be sufficient in the diagnosis for PCa of 10 mm and above<sup>11</sup>. In another study, the bpMRI protocol for clinically significant PCa was shown to have the same diagnostic accuracy as mpMRI<sup>20</sup>. In a similar study, bpMRI focused on the detection of cancer in the anterior fibromuscular stroma and TZ, and they showed that the rates of clinically significant PCa detection by bpMRI were not lower than mpMRI<sup>23</sup>.

Detection of periprostatic invasion (extraprostatic extension, seminal vesicle invasion, bladder invasion) is an important step in treatment planning. Our findings contribute to local staging with bpMRI at this stage. This stage will be more advantageous than mpMRI in shortening the examination time, reducing the cost, and eliminating possible side effects.

Ga68 Prostate Specific Membrane Antigen (Ga68-PSMA) is a new monitoring agent used on PET. Ga68 PSMA-positron emission tomography-computed tomography (PET/CT) is used in the diagnosis, evaluation of the extent of prostate cancer, and treatment follow-up. Ga68 PSMA-PET/CT examination was accepted as the gold standard for demonstrating the presence of invasion. However, this method has some limitations in diagnosis and staging. Ga68 PSMA-PET/CT is confusing and false-positive in conditions such as benign prostatic hypertrophy that increases PSA levels and in conditions such as prostatitis. In this case, Ga68 PSMA-PET/CT can provide additional diagnostic benefits in demonstrating periprostatic invasion of bpMRI, and it can also be used instead of Ga68 PSMA-PET/CT.

The limitations of our study are the fact that the study is retrospective and single center, and the number of patients is low, which is in the first place. The second limitation is that the endorectal coil is not used on MRI sequences. The third limitation is that the images were obtained with a 1.5 T MRI device. Since the second and third limitations will reduce the signal-to-noise ratio, the image quality is low. Another limitation of our study is that the Gallium-68 PSMA-PET/CT examination, which is used in routine practice in demonstrating invasion and metastasis, was not included in the study.

## Conclusion

There is no need to use contrast agent to evaluate periprostatic invasion and to have an idea about local staging in PCa patients. With this method, prolongation of dynamic contrast sequence-based examination,

increase in cost, and undesirable side effects of contrast agent are eliminated. With adequate image quality, T2W and DWI images, radiologists experienced on prostate imaging will not need contrast-enhanced series in the evaluation of periprostatic invasion. We hope that more comprehensive studies will be conducted with images in which the contrast agent is eliminated.

## Funding

The authors declare that they have not received funding.

## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

## References

1. Bjurlin MA, Mendhiratta N, Wysock JS, Taneja SS. Multiparametric MRI and targeted prostate biopsy: improvements in cancer detection, localization, and risk assessment. *Cent European J Urol.* 2016;69:9-18.
2. Stenman UH, Leinonen J, Zhang WM, Finne P. Prostate-specific antigen. *Semin Cancer Biol.* 1999;9:83-93.
3. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al. ESUR prostate MR guidelines 2012. *Eur Radiol.* 2012;22:746-57.
4. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al. Prostate imaging reporting and data system version 2.1: 2019 update of prostate imaging reporting and data system version 2. *Eur Urol.* 2019;76:340-51.
5. Rosenkrantz AB, Shanbhogue AK, Wang A, Kong MX, Babb JS, Taneja SS. Length of capsular contact for diagnosing extraprostatic extension on prostate MRI: assessment at an optimal threshold. *J Magn Reson Imaging.* 2016;43:990-7.
6. Ravary V, Boccon-Gibod L. T3 prostate cancer: how reliable is clinical staging? *Semin Urol Oncol.* 1997;15:202-6.
7. Yu KK, Hricak H, Alagappan R, Chernoff DM, Bacchetti P, Zaloudek CJ. Detection of extracapsular extension of prostate carcinoma with endorectal and phased-array coil MR imaging: multivariate feature analysis. *Radiology.* 1997;202:697-702.
8. Vargas HA, Hötter AM, Goldman DA, Moskowitz CS, Gondo T, Matsumoto K, et al. Updated prostate imaging reporting and data system (PIRADS v2) recommendations for the detection of clinically significant prostate cancer using multiparametric MRI: critical evaluation using whole-mount pathology as standard of reference. *Eur Radiol.* 2016;26:1606-12.



9. Stanzone A, Imbriaco M, Cocozza S, Fusco F, Rusconi G, Nappi C, et al. Erratum to "Biparametric 3t magnetic resonance imaging for prostatic cancer detection in a biopsy-naïve patient population: a further improvement of PI-RADS v2? [Eur J Radiol. 2016;85:2269-74], Eur J Radiol. 2017;87:125.
10. Hansford BG, Peng Y, Jiang Y, Vannier MW, Antic T, Thomas S, et al. Dynamic contrast-enhanced MR imaging curve-type analysis: is it helpful in the differentiation of prostate cancer from healthy peripheral zone? *Radiology*. 2015;275:448-57.
11. Scialpi M, Prosperi E, D'Andrea A, Martorana E, Malaspina C, Palumbo B, et al. Biparametric versus multiparametric MRI with non-endorectal coil at 3T in the detection and localization of prostate cancer. *Anticancer Res*. 2017;37:1263-71.
12. Tamada T, Kido A, Yamamoto A, Takeuchi M, Miyaji Y, Moriya T, et al. Comparison of biparametric and multiparametric MRI for clinically significant prostate cancer detection With PI-RADS version 2.1. *J Magn Reson Imaging*. 2021;53:283-91.
13. Zhang J, Xu L, Zhang G, Zhang X, Bai X, Ji Z, et al. Comparison between biparametric and multiparametric MRI diagnosis strategy for prostate cancer in the peripheral zone using PI-RADS version 2.1. *Abdom Radiol (NY)*. 2022;47:2905-16.
14. Xu L, Zhang G, Shi B, Liu Y, Zou T, Yan W, et al. Comparison of biparametric and multiparametric MRI in the diagnosis of prostate cancer. *Cancer Imaging*. 2019;19:90.
15. Barth BK, De Visschere PJ, Cornelius A, Nicolau C, Vargas HA, Eberli D, et al. Detection of clinically significant prostate cancer: short dual-pulse sequence versus standard multiparametric MR imaging-a multireader study. *Radiology*. 2017;284:725-36.
16. ACR Committee on Drugs and Contrast Media. ACR Manual on Contrast Media Version 10.3; 2018. Available from: <https://www.acr.org/clinical-resources/contrast-manual> [Last accessed on 2019 Jan 08].
17. Verma S, Turkbey B, Muradyan N, Rajesh A, Cornud F, Haider MA, et al. Overview of dynamic contrast-enhanced MRI in prostate cancer diagnosis and management. *AJR Am J Roentgenol*. 2012;198:1277-88.
18. Kitzing YX, Prando A, Varol C, Karczmar GS, Maclean F, Oto A. Benign conditions that mimic prostate carcinoma: MR imaging features with histopathologic correlation. *Radiographics*. 2016;36:162-75.
19. Di Campli E, Delli Pizzi A, Seccia B, Cianci R, d'Annibale M, Colasante A, et al. Diagnostic accuracy of biparametric vs multiparametric MRI in clinically significant prostate cancer: comparison between readers with different experience. *Eur J Radiol*. 2018;101:17-23.
20. Choi MH, Kim CK, Lee YJ, Jung SE. Prebiopsy biparametric MRI for clinically significant prostate cancer detection with PI-RADS version 2: a multicenter study. *AJR Am J Roentgenol*. 2019;212:839-46.
21. Junker D, Steinkohl F, Fritz V, Bektic J, Tokas T, Aigner F, et al. Comparison of multiparametric and biparametric MRI of the prostate: are gadolinium-based contrast agents needed for routine examinations? *World J Urol*. 2019;37:691-9.
22. Schoots IG, Barentsz JO, Bittencourt LK, Haider MA, Macura KJ, Margolis DJ, et al. PI-RADS committee position on MRI without contrast medium in biopsy-naïve men with suspected prostate cancer: narrative review. *AJR Am J Roentgenol*. 2021;216:3-19.
23. Radtke JP, Boxler S, Kuru TH, Wolf MB, Alt CD, Popeneciu IV, et al. Improved detection of anterior fibromuscular stroma and transition zone prostate cancer using biparametric and multiparametric MRI with MRI-targeted biopsy and MRI-US fusion guidance. *Prostate Cancer Prostatic Dis*. 2015;18:288-96.

# Beneficial effects of IVIG treatment on experimental-induced osteoporosis

## Efectos beneficiosos del tratamiento con IVIG en la osteoporosis inducida experimentalmente

Savaş Özdemir<sup>1\*</sup> and Oytun Erbas<sup>2</sup>

<sup>1</sup>Department of Gynecology and Obstetrics, Istanbul Prof. Dr. Cemil Taşçıoğlu City Hospital; <sup>2</sup>Department of Physiology, Demiroğlu Bilim University, Istanbul, Turkey

### Abstract

**Objective:** Estrogen (E2) plays a significant role in postmenopausal osteoporosis, and its deficiency is related to chronic low-grade inflammation. Intravenous immunoglobulin (IVIG) is composed of immunoglobulins derived from the plasma of healthy donors. Numerous anti-inflammatory pathways are responsible for IVIG's anti-inflammatory action. The aim of this study is to investigate the effects of IVIG on experimental-induced osteoporosis. **Materials and methods:** Forty adult female Wistar rats were included in the study. Thirty rats underwent bilateral dorsal ovariectomy. Rats were grouped as Group 1 (n = 10, ovariectomy and saline); Group 2 (n = 10, ovariectomy and E2); Group 3 (n = 10, ovariectomy and IVIG), and Control group (n = 10, no oophorectomy). Histopathological examination of bone tissue, and biochemical analysis for beta-catenin, plasma Tumor Necrosis Factor- $\alpha$ , IL-6, receptor activator of nuclear- $\kappa$ B ligand (RANKL), and osteoprotegerin (OPG) levels were made. **Results:** The IVIG group had increased trabecular number, area, and thickness with increased bone mineral density as well as decreased trabecular separation compared with the saline group. IVIG group had lower serum RANKL and higher serum OPG levels when compared with the saline group. The bone marrow beta-catenin level was significantly higher in the control and ovariectomy + IVIG groups. **Conclusion:** IVIG has beneficial effects on experimentally induced osteoporosis with a possible action on inflammation and RANKL- $\beta$ -catenin pathway.

**Keywords:**  $\beta$ -catenin. IVIG. RANKL. Osteoporosis.

### Resumen

**Objetivo:** El estrógeno juega un papel importante en la osteoporosis posmenopáusica y su deficiencia está relacionada con la inflamación crónica de bajo grado. La inmunoglobulina intravenosa (IGIV) está compuesta por inmunoglobulinas derivadas del plasma de donantes sanos. El objetivo de este estudio es investigar los efectos de IVIG en la osteoporosis inducida experimentalmente. **Materiales y métodos:** 30 ratas se sometieron a ovariectomía dorsal bilateral. Las ratas se agruparon como: Grupo 1 (n = 10, ovariectomía y solución salina); Grupo 2 (n = 10, ovariectomía y estrógeno); Grupo 3 (n = 10, ovariectomía e IVIG) y Grupo Control (n = 10, sin ovariectomía). Se realizó un examen histopatológico del tejido óseo y un análisis bioquímico de los niveles de beta-catenina, factor de necrosis tumoral  $\alpha$  (TNF- $\alpha$ ), IL-6, RANKL y osteoprotegerina (OPG) en plasma. **Resultados:** El grupo IVIG había aumentado el número, el área y el grosor trabecular con una mayor densidad mineral ósea, así como una menor separación trabecular en comparación con el grupo de solución salina. El nivel de beta-catenina en la médula ósea fue significativamente mayor en los grupos de control y de ovariectomía + IVIG. **Conclusión:** IVIG tiene efectos beneficiosos sobre la osteoporosis inducida experimentalmente con una posible acción sobre la inflamación y la vía RANKL- $\beta$ -catenina.

**Palabras clave:**  $\beta$ -catenina. IVIG. RANKL. Osteoporosis.

#### \*Correspondence:

Savaş Özdemir

E-mail: savasozdemir@hotmmail.com

2444-0507/© 2023 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Date of reception: 27-04-2023

Date of acceptance: 08-11-2023

DOI: 10.24875/CIRUE.M23000740

Cir Cir (Eng). 2024;92(5):563-569

Contents available at PubMed

[www.cirugiaycirujanos.com](http://www.cirugiaycirujanos.com)

## Introduction

Uncoupling of bone resorption and production in the same bone region characterizes postmenopausal osteoporosis (PMO). Hormones and bone-derived substances in the bloodstream regulate osteoblastogenesis and osteoclastogenesis<sup>1</sup>. By promoting osteogenic differentiation and decreasing osteoclastogenesis, estrogen (E2) plays a significant role in this process. During PMO, the number of osteoclasts (OC) in the bone may increase by up to 70%, but bone formation may increase to a lower degree, remain steady, or decrease, depending on the stage of menopause<sup>2</sup>. Therefore, PMO is characterized by an increase in bone turnover and a remodeling balance shift toward resorption<sup>3</sup>.

E2 has been demonstrated to interact with a number of immune cells, resulting in chronic low-grade pro-inflammation in individuals lacking in E2<sup>4</sup>.

Chronic inflammatory disorders mediated by immune complexes are often associated with bone loss. These conditions also increase the uncoupling of osteoclast and osteoblast activities, resulting in excessive and pathologic bone resorption<sup>5</sup>.

Intravenous immunoglobulin (IVIG) is a medication composed of immunoglobulins derived from the plasma of thousands of healthy donors. It has been shown to be beneficial in the treatment of a number of autoimmune and chronic inflammatory illnesses. Fc gamma receptors, which bind immunoglobulin G Fc component, and CD209 are two receptors that transmit IVIG signals (also known as DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-Grabbing Non-integrin)<sup>6,7</sup>. Numerous well-established anti-inflammatory pathways are responsible for IVIG's anti-inflammatory action. However, the precise mechanisms behind the immunomodulatory and anti-inflammatory effects of IVIG therapy remain unknown.

Despite extensive studies of the beneficial effects of IVIG on inflammatory diseases, the effects of IVIG on osteoclastogenesis and osteoblastic functions in a sub-inflammatory state like post-menopausal osteoporosis are not known.

Regarding the inflammatory condition in post-menopausal osteoporosis, the aim of this study is to determine the effect of IVIG on bone structure and the markers of osteoblast, osteoclast, and osteocyte functions.

## Materials and methods

### Animals

In this study, 40 female Wistar albino mature rats at weighing 200-250 g, were used. The present study

was approved by the Animal Ethics Committee (Science University, Ethical number: 03220201). The rats used in the experiment were obtained from the Experimental Animal Laboratory of Science University. Rats were fed ad libitum and housed in pairs in steel cages having a temperature-controlled environment ( $22 \pm 2^\circ\text{C}$ ) with 12-h light/dark cycles.

### Experimental protocol

In the present study, 40 adult female Wistar rats were used. Thirty rats underwent bilateral dorsal ovariectomy. Ten rats did not undergo oophorectomy. For the surgical procedure, rats were anesthetized by intraperitoneal injection of a combination of ketamine hydrochloride at a dose of 50 mg/kg and 10 mg/kg xylazine hydrochloric.

Rats were kept at the postmenopausal period for 3 weeks and were ovariectomy rats divided into three groups. Normal control group rats have no ovariectomy and no any therapy. Group 1 (n = 10, ovariectomy and saline) rats were given 1 mL/kg/day saline (0.9% NaCl) by intraperitoneally; Group 2 (n = 10, ovariectomy and E2) rats were given 17-beta-estradiol (E2) 0.5 mg/kg dissolved in sesame oil daily orally by gavage; and Group 3 (n = 10, ovariectomy and IVIG) rats were given IVIG 250 mg/kg/day by intraperitoneally. All treatments were given for 12 weeks.

Twelve weeks later, bone mineral density (BMD) of experimental animals under ketamin anesthesia (50 mg/kg) was measured by Hologic QDR-4500A (DEXA Scan) and a "small animal" program. Measurements were taken with high resolution in two different regions: the left extremity proximal femoral diaphysis and the lumbar vertebrae. Blood samples were collected by cardiac puncture for biochemical analysis and the removal of femurs was performed for histopathological and biochemical examination.

### Histopathological examination of bone tissue

For histological and immunohistochemical studies, all animals were anesthetized by an i.p. of ketamin (40 mg/kg, Alfamine®, Ege Vet, Alfasan International B.V., Holland)/xylazine (4 mg/kg, Alfazyne®, Ege Vet, Alfasan International B.V., Holland) and perfused with 200 mL of 4% formaldehyde in 0.1 M phosphate-buffer saline (PBS).

Following the perfusion procedure, the left femurs of the animals were dissected and kept at room temperature in a 10% formaldehyde fixative for 24 h for histomorphometric analysis. Following fixation, specimens

were placed in 10% formic acid. After decalcification was completed within 28 days, they were taken into routine light microscope follow-up. From the prepared paraffin blocks, transverse sections were obtained in 3-micron thicknesses with a Leica MR 2145 microtome. For morphometric analysis, hematoxylenen-eosin dyed preparations were used<sup>8</sup>.

### **Morphometric analyses**

For each animal, five cross-sections were obtained, from the left hind extremity proximal femoral metaphysis in the paraffine blocks serially, for morphometric analyses. Sections were stained with hematoxylin-eosin, and 20x zoomed digital pictures were taken by an Olympus microscope. To measure trabecular count, trabecular thickness, trabecular area, and trabecular separation, the semi-automatic digital system UTHSCSA Image Tool for Windows Version 1.28 was used. Trabecular measurements were performed at 0.46 mm proximal of the epiphysis plaque and at equal distances from both sides of the cortex in femur preparations. The lengths were calculated as pixels using the program (1 pixel=128 × 10-8 mm)<sup>8</sup>. All measurements were implemented in accordance with the article by Parfitt et al.<sup>9</sup>

### **Morphometric measurements**

For trabecular thickness (μm), measurements were taken at a minimum of 50 different points for every trabecula, and measurements continued to be taken until the mean values became constant. The trabecular count was obtained by counting all trabeculae and each trabecula parallel to each other at 0.46 mm distal to the epiphysis plaque at equal distances from both sides of the cortex. The trabecular area (mm<sup>2</sup>) was calculated by determining the borders of the trabeculae in the region where the trabecular count was determined. Cortical thickness (μm) was calculated by mean values of fifty measurements from 3-micron sections in digital pictures of each preparation. Osteoblast and osteoclast counts were calculated in hematoxylene-eosin dyed preparations with 40x objective zoomed digital pictures using an image analysis program and counting cells around trabeculae 0.5 mm under the epiphysis plaque<sup>8</sup>.

### **Bone marrow biochemical analysis for beta-catenin**

The material obtained was homogenized with a glass homogenizer in 5 volumes of PBS that was 5 times the

volume of the obtained tissue (pH 7.4) and centrifuged at 5.000 g for 15 minutes. Beta-catenin the bone marrow supernatants was measured using commercially available rat enzyme-linked immunosorbent assay (ELISA) kits.

Plasma TNF-α, IL-6, RANKL, and OPG levels were measured using commercially available ELISA kits.

### **Results**

The mean trabecular numbers (number/mm<sup>2</sup>) were significantly higher in the control group compared with ovariectomy + saline, ovariectomy + E2, and ovariectomy + IVIG groups (respectively;  $p < 0.01$ ,  $p < 0.01$  and  $p < 0.05$ ). The mean trabecular number was also significantly higher in the ovariectomy + IVIG group compared with ovariectomy + saline, and ovariectomy + E2 groups (respectively,  $p < 0.01$  and  $p < 0.05$ ). Trabecular area (μm<sup>2</sup>) was significantly higher in the control group compared with ovariectomy + saline, ovariectomy + E2, and ovariectomy + IVIG groups (respectively;  $p < 0.001$ ,  $p < 0.001$  and  $p < 0.05$ ). It was also significantly higher in the ovariectomy + IVIG group compared with ovariectomy + saline and ovariectomy + E2 groups (respectively;  $p < 0.001$  and  $p < 0.05$ ). Trabecular separation was significantly lower in control and IVIG groups compared with ovariectomy + saline and ovariectomy + E2 groups (respectively;  $p < 0.001$ , and  $p < 0.001$ ;  $p < 0.05$  and  $p < 0.001$ ). The mean trabecular thickness (μm) was significantly higher in control group compared with with ovariectomy + saline and ovariectomy + E2 groups (respectively;  $p < 0.01$  and  $p < 0.01$ ). Similarly, it was found to be higher in the IVIG group compared with ovariectomy + saline and ovariectomy + E2 groups (respectively;  $p < 0.01$  and  $p < 0.05$ ). Femoral BMD (g/cm<sup>2</sup>) was significantly higher in the control and IVIG groups compared with the saline group ( $p < 0.01$  and  $p < 0.05$ ). The mean values of lomber vertebra BMD (g/cm<sup>2</sup>) were found to be significantly higher in the control and IVIG groups compared with saline group ( $p < 0.01$  and  $p < 0.05$ ). The data are presented at table 1 (Figs. 1 and 2).

The mean value of plasma TNF-α level (pg/mL) was significantly lower in the control group compared with ovariectomy + saline, ovariectomy + E2, and ovariectomy + IVIG groups (respectively;  $p < 0.001$ ,  $p < 0.001$ , and  $p < 0.01$ ). The mean plasma IL-6 level was significantly lower in the control group compared with ovariectomy + saline, ovariectomy + E2, and ovariectomy + IVIG groups (respectively;  $p < 0.001$ ,  $p < 0.001$ , and  $p < 0.05$ ). The IVIG group had a significantly lower



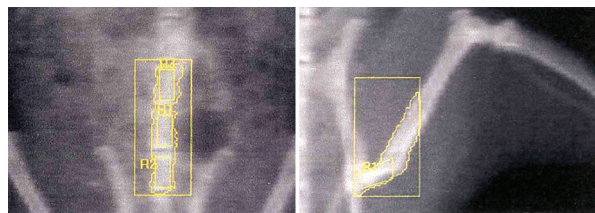
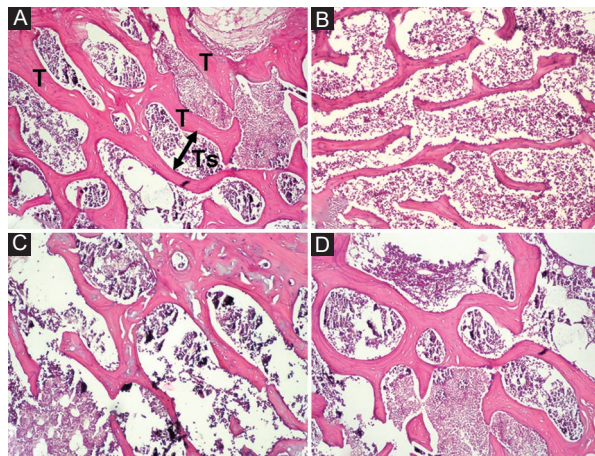
**Table 1. Comparison of bone morphometric analyses and measurements between groups**

Analysis results	Normal control (n = 10)	Ovariectomy + saline (n = 10)	Ovariectomy + E2 (n = 10)	Ovariectomy + IVIG (n = 10)
Trabecular number (number/mm <sup>2</sup> )	12.21 ± 1.03	7.25 ± 0.9*	9.37 ± 1.2 <sup>†</sup>	10.8 ± 0.7 <sup>†</sup>
Trabecular area (μm <sup>2</sup> )	24345.5 ± 2854.2	11457.8 ± 1021.2 <sup>‡</sup>	17365.2 ± 985.7 <sup>†</sup>	20215.3 ± 854.1 <sup>§</sup>
Trabecular separation (μm)	121.3 ± 10.9	244.6 ± 12.8 <sup>‡</sup>	198.5 ± 9.9 <sup>§</sup>	155.8 ± 11.3 <sup>§</sup>
Trabecular thickness (μm)	305.3 ± 24.9	168.2 ± 19.5*	202.1 ± 17.6 <sup>†</sup>	288.5 ± 13.01 <sup>§</sup>
Femoral BMD (g/cm <sup>2</sup> )	0.48 ± 0.11	0.29 ± 0.08*	0.32 ± 0.15	0.35 ± 0.07 <sup>†</sup>
Lomber vertebra BMD (g/cm <sup>2</sup> )	0.30 ± 0.09	0.18 ± 0.12*	0.20 ± 0.05	0.22 ± 0.04 <sup>†</sup>

\*p &lt; 0.05.

<sup>†</sup>p < 0.01.<sup>‡</sup>p < 0.001 (different from the control group).<sup>§</sup>p < 0.001 (different from ovariectomy and saline group).

Results were presented as mean ± SEM. Statistical analyses were performed by one-way ANOVA test.

**Figure 1. Rat DEXA scan.**

**Figure 2. Bone trabeculae (Tb) of rat femur with H&E stain ×20.**  
**A:** normal control group. **B:** ovariectomized group trabecular thinning and widening of trabecular space 15 weeks after ovariectomy. **C:** ovariectomized and estradiol (E2) group restoration of the trabecular thickness. **D:** ovariectomized and IVIG group restoration of the trabecular thickness. T: trabeculae; Ts: trabecular separation.

level of plasma IL-6 compared with the ovariectomy + saline group ( $p < 0.01$ ). The mean plasma RANKL level was significantly lower in the control group compared with ovariectomy + saline, ovariectomy + E2, and ovariectomy + IVIG groups (respectively;  $p < 0.001$ ,

$p < 0.001$ , and  $p < 0.01$ ). It was also significantly lower in ovariectomy + IVIG group and ovariectomy + E2 group compared with ovariectomy + saline group ( $p < 0.01$  and  $p < 0.05$ ). The mean plasma OPG level was significantly higher in the control group compared with ovariectomy + saline, ovariectomy + E2, and ovariectomy + IVIG groups ( $p < 0.01$ ). It was also significantly higher in the ovariectomy + IVIG group and ovariectomy + E2 group compared with the ovariectomy + saline group ( $p < 0.01$  and  $p < 0.05$ ). The mean levels of bone marrow beta-catenin level (pg/mg protein) were significantly higher in control and ovariectomy + IVIG groups compared with ovariectomy + saline and ovariectomy + E2 groups (respectively;  $p < 0.01$ , and  $p < 0.01$ ;  $p < 0.01$  and  $p < 0.01$ ) (Table 2).

## Discussion

In the current study, the administration of IVIG was shown to have favorable benefits, including an increase in trabecular number, trabecular area, trabecular thickness, femoral BMD, and lumbar vertebra BMD, and a decrease in trabecular separation. In the current investigation, it was shown that IVIG is equally efficient as E2 in treating experimentally induced osteoporosis. Moreover, IVIG therapy has been demonstrated to be better in various osteoporosis-related parameters.

Osteoporosis is the most frequent metabolic bone disease, affecting 50% of women and 30% of men in their sixth and seventh decades of life<sup>10</sup>. Osteoporosis is characterized by uncoupled bone resorption, which results in a loss of bone mass. Continuous bone remodeling is



**Table 2. Comparison of immune parameters, RANKL, OPG, and bone marrow beta-catenin between groups**

Parameters	Normal control (n = 10)	Ovariectomy + saline (n = 10)	Ovariectomy + E2 (n = 10)	Ovariectomy + IVIG (n = 10)
Plasma TNF- $\alpha$ level (pg/mL)	30.1 $\pm$ 9.5	97.4 $\pm$ 14.8*	65.6 $\pm$ 12.9 <sup>†</sup>	55.7 $\pm$ 9.8 <sup>‡</sup>
Plasma IL-6 level (pg/mL)	405.5 $\pm$ 28.5	644.1 $\pm$ 11.3*	542.7 $\pm$ 8.8 <sup>†</sup>	487.5 $\pm$ 13.5 <sup>‡</sup>
Plasma RANKL level (pg/mL)	60.3 $\pm$ 2.24	145.4 $\pm$ 4.95 <sup>§</sup>	114.1 $\pm$ 5.67 <sup>†</sup>	108.03 $\pm$ 6.4 <sup>‡</sup>
Plasma OPG level (pg/mL)	20.5 $\pm$ 1.09	9.8 $\pm$ 1.1*	14.3 $\pm$ 0.8 <sup>†</sup>	13.2 $\pm$ 1.5 <sup>‡</sup>
Bone Marrow Beta-catenin level (pg/mg protein)	21.4 $\pm$ 5.5	11.6 $\pm$ 2.9*	19.5 $\pm$ 1.5 <sup>†</sup>	25.8 $\pm$ 2.3 <sup>‡</sup>

\*p &lt; 0.05.

<sup>†</sup>p < 0.01.<sup>‡</sup>p < 0.001 (different from ovariectomy and saline group).<sup>§</sup>p < 0.001 (different from the control group).Results were presented as mean  $\pm$  SEM. Statistical analyses were performed by one-way ANOVA test.

a coordinated procedure for repairing microfractures and maintaining bone mass.

The two primary cell types involved in bone remodeling are bone-resorbing OC and bone-forming osteoblasts (OB). In the past 10 years, bone-embedded osteocytes have emerged as critical regulators. OC are multinucleated monocytic cells whose differentiation is controlled by the nuclear factor-kB receptor activator (RANK) and RANKL. Multiple signaling mechanisms, including WNT/b-catenin and BMP, govern OB formation from the mesenchymal stem cell lineage. During remodeling, the OC and OB form the bone remodeling unit<sup>11</sup>.

E2 deficiency has been associated to a predictor of future osteoporosis in postmenopausal women for about eight decades. Despite extensive investigation, the mechanism behind E2 deficiency-induced accelerated bone resorption is unclear<sup>12</sup>. Menopause and aging have been linked to reduced calcium absorption, deterioration of renal function, and changes in vitamin D metabolism<sup>13</sup>.

In our study, TNF alpha and IL6 levels increased after oophorectomy. This elevation was greatest in the oophorectomy+ saline group and lower in the IVIG group.

The adaptive immune system has been shown in both human and animal models to have a critical role in the development of PMO. After detecting the influence of T-cell-derived cytokines on bone, Arron and Choi created the term osteoimmunology in 2000<sup>14</sup>. Proinflammatory cytokines produced by T cells, such as TNF and interleukin-17A, have proresorptive properties<sup>15</sup>. Chronic inflammation induced by an E2 deficiency may aggravate osteoporosis and lead to other complications<sup>16</sup>.

Takayanagi et al. discovered that IFN-g generated by T cells may block RANKL signaling during OC formation<sup>17</sup>. Because Th1 cells produce a large amount

of IFN-g, it was assumed that inflammatory bone loss was induced by Th1 cells.

IL-17A has been demonstrated to induce significant bone loss, especially in those with autoimmune disorders<sup>17</sup>. TNF has been shown to stimulate osteoclastogenesis by directly acting on OC<sup>18</sup>. Patients with rheumatoid arthritis, inflammatory bowel disease, and chronic lung disease are more likely to have osteoporosis<sup>19</sup>. An increase in local cytokines may accelerate bone resorption in these circumstances<sup>20</sup>.

In the current study, the IVIG group had lower serum RANKL levels and higher serum OPG levels than the saline group.

RANKL is a cytokine that belongs to the TNF superfamily. The RANKL receptor, known as RANK, is strongly linked with CD40. It is well known that genetic deletion or mutation of RANKL causes severe osteoporosis, which is accompanied with a total deficiency on OC<sup>21</sup>. RANKL stimulation with RANK has a detrimental effect on OC development. TNF receptor-associated factors and kinases are activated when RANKL binds to RANK<sup>22</sup>. OPG is a RANKL receptor. While binding RANKL, OPG inhibits RANKL/RANK interaction and promotes bone resorption by blocking OC formation<sup>23</sup>. Experimental investigations have revealed that genetic deletion of OPG causes osteoporosis<sup>24</sup>. It is thought that an increase in RANKL and a concurrent reduction in OPG is a key risk factor for bone illnesses such as osteoporosis<sup>25</sup>. There have been two earlier studies that looked at the relationships between IVIG and RANKL. In addition to its immunosuppressive effects, Lee and colleagues revealed that IVIG directly suppressed osteoclastogenesis through a mechanism that included RANK signaling suppression<sup>26</sup>. Kim and colleagues discovered that IVIG reduced osteoclastogenesis when monocytes were cocultured with Th17 cells<sup>27</sup>.

Although both studies demonstrated the effects of IVIG on RANKL in cell culture, they conceptually supported the positive benefits of IVIG in osteoporosis therapy.

In our research, bone marrow beta-catenin levels were higher in the IVIG group than in the saline group and Wnt signaling is widely known to have a function in bone remodeling and development. The Wnt/-catenin pathway is a key component of this signaling system<sup>28</sup>. As the quantity of -catenin grows, it translocates into the nucleus and activates the genes Lef1 and Tcf1<sup>29</sup>. Following this stimulation, osteoblastic differentiation and bone production ensue<sup>30</sup>. As a result, this route is crucial for bone. Furthermore, there has been therapeutic use of the Wnt pathway; sclerostin - which neutralizes antibodies<sup>31</sup>. These antibodies are currently accessible for clinical usage in the treatment of osteoporosis<sup>32</sup>. Nonetheless, these antibody medications are expensive, have a one-year shelf life, and have considerable vascular adverse effects. As a result, the application of these antibodies in clinical practice is thought to be restricted<sup>33</sup>. There is just one research in the literature that looks at the relationship between IVIG and -catenin. Kranam and colleagues demonstrated that therapeutic normal IgG IVIG treatment resulted in the activation of the -catenin pathway<sup>34</sup>. Our findings validated the previous work, and we also established for the first time that IVIG therapy had a beneficial impact on -catenin in experimentally generated osteoporosis.

In conclusion, this is the first study to demonstrate the protective benefits of IVIG on experimentally induced osteoporosis. Mechanism activities are linked to RANKL, anti-inflammation, and the -catenin pathway. Following more research, anti-inflammatory medicines impacting these pathways, such as IVIG, may be regarded a potential agent in the treatment of osteoporosis without major adverse effects.

## Funding

The author declares no funding was received for this study.

## Conflicts of interest

The author declares no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical

research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

## References

- Romas E, Martin TJ. Cytokines in the pathogenesis of osteoporosis. *Osteoporos Int*. 1997;7:47-53.
- Eriksen EF, Hodgson SF, Eastell R, Riggs BL, Cedel SL, O'Fallon WM. Cancellous bone remodeling in type I (postmenopausal) osteoporosis: quantitative assessment of rates of formation, resorption, and bone loss at tissue and cellular levels. *J Bone Miner Res*. 1990;5:311-9.
- Garnero P, Sornay-Rendu E, Chapuy MC, Delmas PD. Increased bone turnover in late postmenopausal women is a major determinant of osteoporosis. *J Bone Miner Res*. 1996;11:337-49.
- Ralston SH. Analysis of gene expression in human bone biopsies by polymerase chain reaction: evidence for enhanced cytokine expression in postmenopausal osteoporosis. *J Bone Miner Res*. 2009;9:883-90.
- Schett G, Gravallesse E. Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. *Nat Rev Rheumatol*. 2012;8:656-64.
- Schwab I, Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? *Nat Rev Immunol*. 2013;13:176-89.
- Anthony RM, Kobayashi T, Wermeling F, Ravetch JV. Intravenous gammaglobulin suppresses inflammation through a novel TH2 pathway. *Nature*. 2011;475:110-3.
- Eminov E, Hortu I, Akman L, Erbas O, Yavasoglu A, Cirpan T. Exenatide preserves trabecular bone microarchitecture in experimental ovariectomized rat model. *Arch Gynecol Obstet*. 2018;297:1587-93.
- Parfitt AM, Drezner MK, Glorieux FH, Kanis JA, Malluche H, Meunier PJ, et al. Bone histomorphometry: standardization of nomenclature, symbols, and units: report of the ASBMR histomorphometry nomenclature committee. *J Bone Miner Res*. 2009;24:595-610.
- Kenkre J, Bassett J. The bone remodelling cycle. *Ann Clin Biochem*. 2018;55:308-27.
- Albright F, Smith PH, Richardson AM. Postmenopausal osteoporosis: its clinical feature. *JAMA*. 1941;116:2465-74.
- Riggs BL, Khosla S, Melton LJ 3rd. A unitary model for involutional osteoporosis: estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. *J Bone Miner Res*. 1998;13:763-73.
- Eastell R, Yergey AL, Vieira NE, Cedel SL, Kumar R, Riggs BL. Interrelationship among vitamin D metabolism, true calcium absorption, parathyroid function, and age in women: Evidence of an age-related intestinal resistance to 1,25-dihydroxyvitamin D action. *J Bone Miner Res*. 2009;6:125-32.
- Arron JR, Choi Y. Bone versus immune system. *Nature*. 2000;408:535-6.
- Aurora R. Confounding factors in the effect of gut microbiota on bone density. *Rheumatology (Oxford)*. 2019;58:2089-90.
- Das M, Cronin O, Keohane DM, Cormac EM, Nugent H, Nugent M, et al. Gut microbiota alterations associated with reduced bone mineral density in older adults. *Rheumatology*. 2019;58:2295-304.
- Takayanagi H, Ogasawara K, Hida S, Chiba T, Murata S, Sato K, et al. T-cell-mediated regulation of osteoclastogenesis by signalling cross-talk between RANKL and IFN- $\gamma$ . *Nature*. 2000;408:600-5.
- Zhao B, Grimes SN, Li S, Hu X, Ivashkiv LB. TNF-induced osteoclastogenesis and inflammatory bone resorption are inhibited by transcription factor RBP-J. *J Exp Med*. 2012;209:319-34.
- Moran CA, Neale Weitzmann M, Ofotokun I. Bone loss in HIV infection. *Curr Treat Options Infect Dis*. 2017;9:52-67.
- Tang M, Lu L, Yu X. Interleukin-17A interweaves the skeletal and immune systems. *Front Immunol*. 2021;11:625034.

21. Dougall WC, Glaccum M, Charrier K, Rohrbach K, Brasel K, De Smedt T, et al. RANK is essential for osteoclast and lymph node development. *Genes Dev.* 1999;13:2412-24.
22. Yao Z, Getting SJ, Locke IC. Regulation of TNF-induced osteoclast differentiation. *Cells.* 2021;11:132.
23. Boyce BF, Xing L. Biology of RANK, RANKL, and osteoprotegerin. *Arthritis Res Ther.* 2007;9:S1.
24. Bucay N, Sarosi I, Dunstan CR, Morony S, Tarpley J, Capparelli C, et al. Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. *Genes Dev.* 1998;12:1260-8.
25. Hofbauer LC. Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases. *JAMA.* 2004;292:490-5.
26. Lee MJ, Lim E, Mun S, Bae S, Murata K, Ivashkiv LB, et al. Intravenous immunoglobulin (IVIG) attenuates TNF-induced pathologic bone resorption and suppresses osteoclastogenesis by inducing A20 expression. *J Cell Physiol.* 2016;231:449-58.
27. Kim KW, Kim HR, Kim BM, Won JY, Lee KA, Lee SH. Intravenous immunoglobulin controls Th17 cell-mediated osteoclastogenesis. *Immune Netw.* 2019;19:e27.
28. Krishnan V, Bryant HU, MacDougald OA. Regulation of bone mass by Wnt signaling. *J Clin Invest.* 2006;116:1202-9.
29. Baron R, Kneissel M. WNT signaling in bone homeostasis and disease: from human mutations to treatments. *Nat Med.* 2013;19:179-92.
30. Leucht P, Minear S, Ten Berge D, Nusse R, Helms JA. Translating insights from development into regenerative medicine: the function of Wnts in bone biology. *Semin Cell Dev Biol.* 2008;19:434-43.
31. van Dinther M, Zhang J, Weidauer SE, Boschert V, Muth EM, Knappik A, et al. Anti-sclerostin antibody inhibits internalization of sclerostin and sclerostin-mediated antagonism of Wnt/LRP6 signaling. *PLoS One.* 2013;8:e62295.
32. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med.* 2016;375:1532-43.
33. Asadipooya K, Weinstock A. Cardiovascular outcomes of romosozumab and protective role of alendronate. *Arterioscler Thromb Vasc Biol.* 2019;39:1343-50.
34. Karnam A, Rambabu N, Das M, Bou-Jaoudeh M, Delignat S, Käsermann F, et al. Therapeutic normal IgG intravenous immunoglobulin activates Wnt- $\beta$ -catenin pathway in dendritic cells. *Commun Biol.* 2020;3:96.

# Effect of laparoscopic gastric sleeve vs. laparoscopic gastric bypass in Roux-Y on long-term weight loss in obese mexican population

*Efecto de la manga gástrica laparoscópica vs. el bypass gástrico laparoscópico en Y de Roux sobre la pérdida ponderal a largo plazo en población mexicana con obesidad*

David Lomeli-Reyes<sup>1\*</sup>, Gonzalo M. Torres-Villalobos<sup>2,3</sup>, José M. Correa-Rovelo<sup>2</sup>, Alejandro Díaz Girón-Gidí<sup>2</sup>, Amado J. Athié-Athié<sup>2</sup>, and Perla X. López-Almanza<sup>1</sup>

<sup>1</sup>Posgrado de Cirugía General, Hospital Médica Sur, Facultad Mexicana de Medicina, Universidad La Salle; <sup>2</sup>Departamento de Cirugía General, Hospital Médica Sur; <sup>3</sup>Departamento de Cirugía Experimental, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Mexico City, Mexico

## Abstract

**Objective:** Compare the weight loss results between long-term procedures up to 5 years, after undergoing MGL and RYGB in Mexican patients with obesity and associated comorbidity. The most common bariatric surgical procedures worldwide are, laparoscopic gastric sleeve (MGL) and laparoscopic Roux-en-Y gastric bypass (RYGB), as a treatment for weight loss and remission of comorbidity associated with obesity; however, they are the long-term weight loss results in the Mexican population are unknown. **Method:** Retrospective, observational cohort of patients with obesity undergoing MGL or RYGB in a private hospital Medica Sur, in Mexico City, in the period from 2013 to 2021. Instrumental variables analysis and standardized mean differences were used to calculate outcomes up to 5 years at 5 follow-up visits (S1-S5), at 7 days, 2 months, 6 months, 10 months and 2-5 years after surgery, to compare results of the groups. **Results:** 104 patients were included in two groups: 31 (30.09%) with MG and 73 (70.87%) with RYGB. The last follow-up (S5), the MG group recorded a mean EW 9.61 kg, EW% 12.72% and EWL% 73.50%, and the RYGB group EW 10.1 kg, EW% 14.72% and EWL% 70.41%. **Conclusions:** No significant difference was found between groups for long-term EW loss ( $p = 0.082$ ); however, there is a greater decrease in weight loss in RYGB at 6-12 months compared to MGL.

**Keywords:** Bariatric surgery. Metabolic surgery. Obesity. Sleeve gastrectomy. Roux-en-Y gastric bypass.

## Resumen

**Objetivo:** Comparar los resultados de pérdida de peso con los procedimientos MGL y BGYRL a largo plazo (hasta 5 años) en pacientes mexicanos con obesidad y comorbilidad asociada. Son dos los procedimientos quirúrgicos bariátricos más frecuentes en todo el mundo: la manga gástrica lapa-ros-cópica (MGL) y el bypass gástrico en Y de Roux laparoscópico (BGYRL); ambos como tratamiento para pérdida ponderal y remisión de la comorbilidad asociadas a la obesidad. Sin embargo, se desconocen los resultados de pérdida de peso a largo plazo en la población mexicana. **Método:** Cohorte retrospectiva, observacional, de pacientes con obesidad sometidos a MGL o BGYRL en el hospital privado Médica Sur, de Ciudad de México, en el período de 2013 a 2021. Se utilizó el análisis de variables instrumentales y diferencias de medias estandarizadas para calcular los desenlaces hasta 5 años posquirúrgicos en cinco consultas de seguimiento (S1-S5) a los 7 días, 2 meses, 6 meses, 10 meses y 2-5 años posquirúrgicos, para comparar los resultados de los grupos. **Resultados:** Se incluyeron 104

### \*Correspondence:

David Lomeli-Reyes  
E-mail: dlomeliirey@gmail.com

Date of reception: 02-11-2023  
Date of acceptance: 16-03-2024  
DOI: 10.24875/CIRUE.M24000741

Cir Cir (Eng). 2024;92(5):570-575  
Contents available at PubMed  
www.cirurgiaycirujanos.com

2444-0507/© 2024 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

*pacientes en dos grupos: 31 (30.09%) con MG y 73 (70.87%) con BGYR. En el último seguimiento (S5), el grupo de MG registró media de EW 9.61 kg, EW% 12.72% y EWL% 73.50%, y el grupo BGYR tuvo EW 10.1 kg, EW% 14.72% y EWL% 70.41%. Conclusiones: No se encontró diferencia significativa entre grupos para pérdida de EW a largo plazo ( $p = 0.082$ ); sin embargo, hay una mayor disminución de pérdida ponderal en los pacientes con BGYR a los 6-12 meses en comparación con los tratados con MGL.*

**Palabras clave:** Cirugía bariátrica. Cirugía metabólica. Obesidad. Gastrectomía en manga. Bypass gástrico en Y de Roux.

## Introduction

For decades, obesity has become a public health issue, and its global incidence and prevalence continue to rise, along with the costs of its treatment and chronic repercussions. The excessive accumulation of body fat (typically 20% above the ideal weight) will eventually affect health and lead to damage that may not be reversible, potentially resulting in multiple associated comorbidities<sup>1</sup>, as well as a significant deterioration in quality of life<sup>2</sup>. It is estimated that by 2030, 57.8% of the global population (3.3 billion people) will have overweight or obesity<sup>3</sup>. Significant improvements in health-related quality of life have been demonstrated in patients who underwent bariatric surgery<sup>4</sup>.

Laparoscopic bariatric surgery is currently the surgical treatment of choice for obesity and its related comorbidities, with gastric sleeve (GS) being the most widely performed procedure today, compared to gastric bypass (GB) as the most widely practiced worldwide<sup>5</sup>.

In postoperative follow-up, it is crucial to report data under a standardized outcomes reporting system, such as the one provided by the American Society for Metabolic and Bariatric Surgery (ASMBS), which includes long-term follow-up of at least 5 years after the procedure, as well as bariatric variables such as excess weight (EW) and the percentage of excess weight loss (EWL%)<sup>6</sup>.

A meta-analysis comparing laparoscopic gastric sleeve (LGS) and laparoscopic Roux-en-Y gastric bypass (LRYGB) in patients with a body mass index (BMI) > 50 kg/m<sup>2</sup> showed that LRYGB achieved better weight loss after 6 to 12 months and a greater resolution of dyslipidemia 1 year after the intervention<sup>7</sup>.

In the observational follow-up of the SLEEVEPASS trial at 10 years, which was a multicenter randomized clinical trial, LRYGB showed an 8.4% greater EWL% vs GS. A meta-analysis of 18 studies did not find statistical significance between EWL with GS vs. LRYGB<sup>8</sup>. In a 4-year follow-up, GS had fewer reinterventions, hospitalizations, complications, lower general health-care costs, and less mortality<sup>9</sup> compared to patients

who underwent LRYGB<sup>10</sup>. However, at 2 years, revision surgery was more frequent with GS.

There are different types and degrees of obesity: severe, morbid, or grade III. One of the studies with the longest follow-up, lasting 12 years for 90% of its initial population, showed that patients who underwent LRYGB maintained an average weight loss of 35 kg in follow-up, compared to 0 to 2.9 kg in the non-surgical group<sup>11</sup>. LRYGB is generally more effective than GS, with total remission of obesity-related comorbidities<sup>12</sup>. The short-term morbidity and mortality with both procedures are very low, and if complications arise, they are typically minor within the first 6 months<sup>13</sup>.

The success of bariatric surgery lies in the high rate of complete or partial remission of obesity-associated comorbidities, preventing complications, late effects, and related diseases, as well as improving quality of life<sup>14</sup> by achieving sustained weight loss<sup>15</sup>. Understanding the benefits and long-term outcomes of bariatric procedures is crucial due to their significant impact on morbidity and mortality associated with metabolic syndrome and obesity<sup>16</sup>.

The objective of this study was to compare weight loss up to 5 years across five postoperative follow-ups in Mexican patients who underwent the main bariatric procedures.

## Method

This was a retrospective, observational study of obese patients who underwent laparoscopic bariatric surgery from March 2013 to September 2021 at the third-level hospital Médica Sur in Mexico City. A non-probabilistic convenience sampling was used, selecting consecutive cases during the study period according to inclusion criteria. Clinical records, both physical and electronic, were used, and G\*Power from Heinrich Heine University Düsseldorf was employed for statistical power analysis, with a patient population of 120, who underwent LGS and LRYGB, with a 95% confidence interval and an ideal sample size of 89 patients.

All patients received mechanical thromboprophylaxis prior to surgery and pharmacological thromboprophylaxis until hospital discharge.



The study included patients (Fig. 1) with morbid obesity/grade III (BMI > 40 kg/m<sup>2</sup>) and grade II obesity (BMI > 35 kg/m<sup>2</sup>) with obesity-related comorbidities (systemic hypertension, type 2 diabetes, obstructive sleep apnea syndrome, dyslipidemia), and with pre-operative cardiological assessment without contraindications. Patients who had undergone revision surgery (secondary procedure), had prior intra-abdominal surgery, or had grade II obesity without comorbidity were excluded. Variables considered were age, sex, BMI, and comorbidity, and variables compared included EW, excess weight percentage (EW%), and EWL% between groups.

Patients were followed up through five consultations after the procedure: the first follow-up occurred with a mean of 10 days (n = 104), the second with a mean of 72 days (n = 97), the third with a mean of 235 days (n = 79), the fourth with a mean of 317 days (n = 55), and the fifth with a mean of 669 days (n = 38) for both the GS and LRYGB groups, with comparisons made at each follow-up. All results are presented as means, with standard deviation (SD) and a 95% confidence interval (95%CI). Anthropometric measurements and postoperative bariatric parameters were collected at each follow-up.

For the LRYGB surgical technique, a 20 cm<sup>3</sup> gastric pouch was created with a 100 cm biliary limb and a 150 cm alimentary limb, and a 36-Fr calibration tube was used, along with transoperative endoscopy. For GS, antrectomy was performed up to 1 cm lateral to the His angle, and calibration was done with a 40-Fr tube, with transoperative endoscopy used as well.

To avoid biases in the surgical technique, the procedures were performed by the same surgeon and surgical team.

Statistical analyses were conducted using the SPSS software (Statistical Package for the Social Sciences) version 25.0. Categorical variables are presented as frequencies and percentages, and numerical variables as means and SD as measures of dispersion. The Kolmogorov-Smirnov test was used to verify normal data distribution, and Levene's test was used to confirm homoscedasticity. A paired t-test was applied for analysis of numerical variables within the same group over time. A Student's t-test was used to explore differences between groups over time. A two-step transformation method was applied for variables that did not follow a normal distribution. Values with  $p < 0.05$  were considered statistically significant.

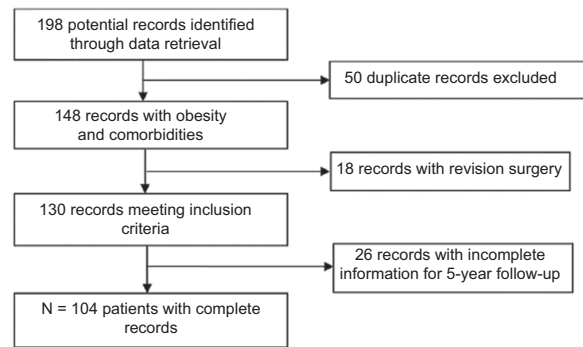


Figure 1. Flowchart of patient inclusion.

## Results

A total of 104 patients were included, divided into the LRYGB group and the LGS group. The demographic data (Table 1) showed a significant difference between the groups in the variables of female sex, presence of dyslipidemia, and gastroesophageal reflux disease ( $p < 0.001$ ). Regarding EW, EW%, and EWL%, no statistically significant differences were found between the groups in the recorded follow-ups (Table 2).

Greater weight loss was observed in the LRYGB group at 6-12 months compared to the LGS group; however, no significant differences were found between the weight, excess weight, or excess weight loss in the follow-ups between the two groups.

With the anthropometric data recorded during follow-up, the means of weight (Fig. 2), EW (Fig. 3), EWL% (Fig. 4), EW% (Fig. 4), and BMI (Fig. 5) were plotted, from the start of the preoperative protocol to the last postoperative follow-up (Fig. 5).

## Discussion

There are numerous treatments vs obesity in response to the growing global incidence, but bariatric surgery remains the most effective method. It is known that, in the long term, up to 10 years post-surgery, LRYGB is the most effective procedure; however, the most widely performed surgery worldwide today is LGS. This highlights the relevance of generating comparative results between both procedures in the long term.

Several studies have identified greater weight loss in patients with LRYGB compared to GS, including controlled clinical trials, systematic reviews, and meta-analyses. A meta-analysis<sup>6</sup> found no difference in weight loss with follow-up > 5 years for both procedures.

**Table 1. Baseline Demographic Characteristics of the Included Population**

Characteristics	LRYGB (n = 73; 70.87%)	LGS (n = 31; 30.09%)	p
Women	52 (71.2%)	16 (51.6%)	< 0.001
Men	21 (28.8%)	15 (48.4%)	0.472
Age, years, mean (SD)	43.6 (14.18)	43.25 (15.31)	0.914
Weight, kg, mean (SD)	115.91 (26.71)	111.54 (22.02)	0.389
Height, m, mean (SD)	1.69 (0.19)	1.71 (0.16)	0.552
BMI, kg/m <sup>2</sup> , mean (SD)	43.03 (7.56)	39.24 (5.27)	0.004
Type II Diabetes Mellitus	22 (29.7%)	11 (35.5%)	0.136
Hypertension	21 (28.5%)	11 (35.5%)	0.171
Dyslipidemia	25 (33.8%)	5 (16.1%)	< 0.001
OSAS	9 (12.2%)	4 (12.9%)	0.072
GERD	3 (4.1%)	0 (0.0%)	< 0.001
Metabolic Syndrome	49 (66.2%)	21 (67.7%)	0.057

LRYGB: laparoscopic Roux-en-Y gastric bypass; SD: standard deviation;  
GERD: gastroesophageal reflux disease; BMI: body mass index; LGS: laparoscopic  
gastric sleeve; OSAS: obstructive sleep apnea syndrome.

In our study, the number of procedures was higher for the LRYGB group than for the LGS group, contrary to what is described in the literature and current global trends. This discrepancy was due to the earlier years during which patients underwent bariatric surgery, with initially higher volumes, followed by a frequency reversal, making LGS now the most widely performed procedure, with no variations in the previously described surgical techniques. Demographic variables were similar between the two groups, as was comorbidity, with no significant differences. Three complications occurred, including postoperative bleeding from the staple line in the LGS group, all of which were resolved during the same hospitalization.

In our retrospective cohort, numerous anthropometric variables were collected over five follow-up visits, with an average of 669 postoperative days at the last follow-up. Weight loss was similar in both groups, though greater weight loss was observed in the first 6-12 postoperative months in the LRYGB group (6).

At the final follow-up, the LGS group recorded an EW of 9.61 kg, EW% of 12.72%, and EWL% of 73.50%, while the LRYGB group recorded an EW of 10.1 kg, EW% of 14.72%, and EWL% of 70.41%, with no significant difference.

**Table 2. Postoperative Follow-ups (S1-S5)**

	S1 (x 10 days)			S1 (x 72 days)			S1 (x 235 days)			S1 (x 317 days)			S1 (x 669 days)		
	LRYGB	LGS	p	LRYGB	LGS	p	LRYGB	LGS	p	LRYGB	LGS	p	LRYGB	LGS	p
EW (kg)															
$\bar{x}$	40.44-48.75	32.28-40.79	0.083	31.94-40.43	26.09-33.05	0.185	23.35-32.83	16.76-25.98	0.417	16.98-25.66	13.32-17.62	0.141	10.13-17.03	9.61-14.75	0.082
SD	7.59	7.94		8.22	5.9		7.8	7.72		6.77	3.06		5.56	4.09	
95%CI	6.99-9.06	7.43-9.58		6.06-11.01	4.72-9.21		7.39-11.56	6.74-11.68		6.69-10.66	2.45-6.16		4.85-8.94	3.49-7.77	
EW%															
$\bar{x}$	59.93-66.16	44.92-50.0	0.068	47.42-66.16	36.31-45.9	0.138	34.92-48.86	23.42-36.18	0.233	24.86-38.08	18.26-24.26	0.086	14.72-25.32	12.72-16.98	0.061
SD	6.85	4.02		16.02	7.69		11.81	10.23		10.85	4.4		8.43	3.81	
95%CI	4.62-7.82	3.63-6.58		8.91-16.67	6.66-12.51		11.04-16.83	9.62-15.87		10.14-16.28	3.33-8.66		7.5-13.69	3.69-10.2	
EWL%															
$\bar{x}$	9.18-19.86	13.57-24.56	0.623	19.50-38.37	23.24-39.90	0.401	38.66-56.84	39.63-65.32	0.883	53.06-70.89	67.75-78.98	0.129	14.72-70.41	12.72-73.50	0.161
SD	10.6	10.86		16.28	12.09		17.04	24.68		15.03	11.21		47.13	39.02	
95%CI	7.5-13.84	6.63-15.34		15.41-22.32	12.07-21.24		13.65-22.7	18.20-33.16		14.07-21.58	10.92-20.14		42.06-69.30	33.93-87.61	

SD: standard deviation; EW: excess weight; EW%: percentage of excess weight; EWL%: percentage of excess weight loss; 95%CI: 95% confidence interval.

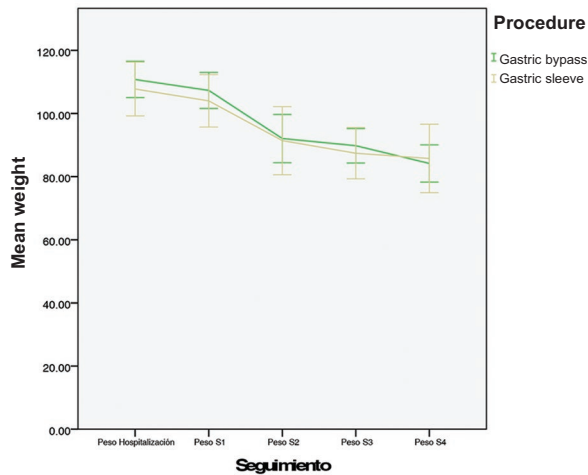


Figure 2. Postoperative follow-up of weight loss (mean weight).

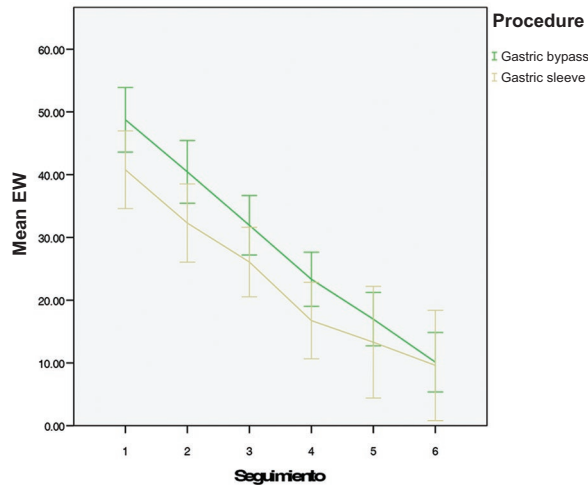


Figure 3. Postoperative follow-up of excess weight.

Analyses between groups across various follow-up records showed no statistically significant difference in weight loss at 20-month follow-up, with a 100% retention rate; however, the number of patients who discontinued follow-up visits later varied, with a tendency to drop out.

A limitation of this retrospective cohort study, given its nature, is the long-term follow-up, with gaps in record-keeping leading to the exclusion of some patients. Additionally, the year of patient selection was not the same, and the cohort was not homogeneous across both groups; however, the five postoperative follow-up visits were consistent. It is essential to

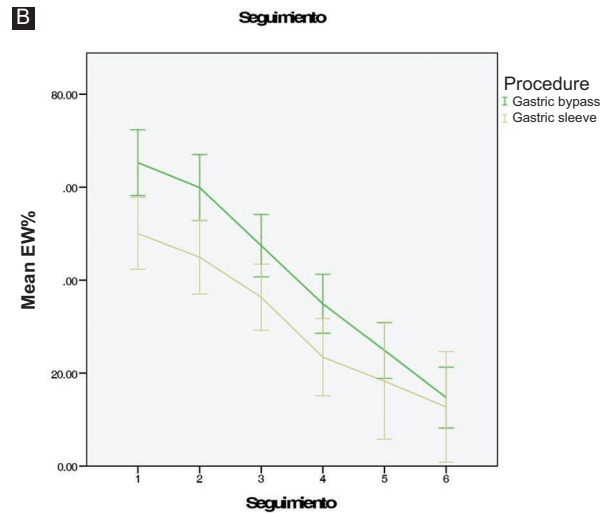
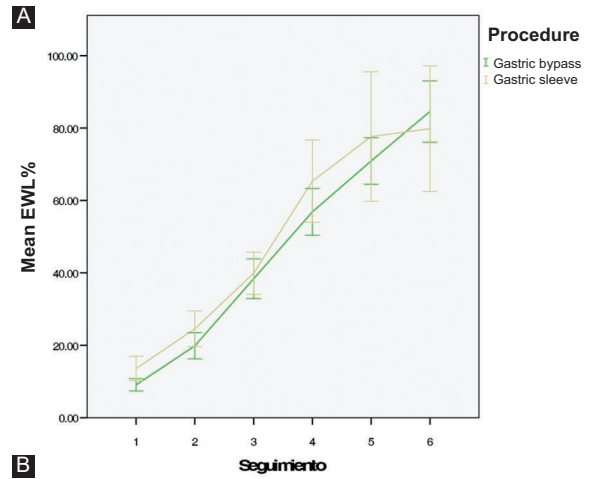


Figure 4. A) Postoperative follow-up of excess weight loss percentage (EWL%). B) Postoperative follow-up of excess weight percentage (EW%).

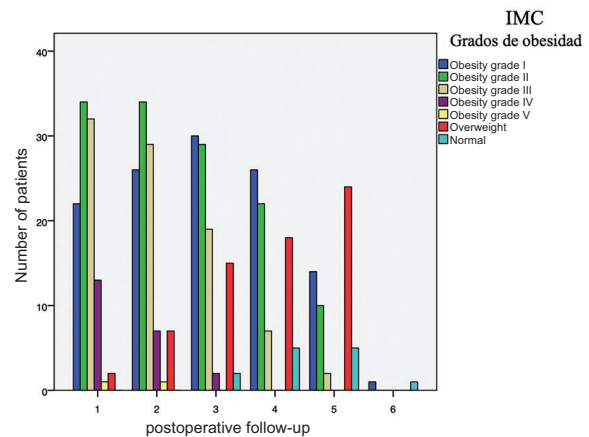


Figure 5. Comparison of body mass index in the postoperative follow-up.

highlight the varying adherence to follow-up visits among the study participants.

## Conclusions

The GS procedure had the same long-term weight loss in the Mexican population as LRYGB, with the latter being more effective in weight loss within the first 6-12 months. No differences were found regarding the resolution of comorbidity between the groups, and there was no significant difference in complications and reinterventions. Currently, there is no effective strategy for long-term postoperative patients, so better measures need to be implemented for the follow-up of obese patients undergoing bariatric surgery to achieve optimal postoperative control and follow-up, ensuring more reliable long-term results, as well as improving weight control and enhancing the quality of life for patients while continuing the complete remission of obesity-related comorbidities.

## Acknowledgments

The authors would like to thank Hospital Médica Sur for being our home and the School of Medicine of Universidad La Salle for their academic support in conducting this study.

## Funding

None declared.

## Conflicts of interest

None declared.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

## References

- Andersen JR, Aasprang A, Karlén TI, Natvig GK, Våge V, Kolotkin RL. Health-related quality of life after bariatric surgery: a systematic review of prospective long-term studies. *Surg Obes Relat Dis*. 2015;11:466-73.
- Grönroos S, Helmiö M, Juuti A, Tiusanen R, Hurme S, Löytyniemi E, et al. Effect of laparoscopic sleeve gastrectomy vs Roux-en-Y gastric bypass on weight loss and quality of life at 7 years in patients with morbid obesity: the SLEEVEPASS randomized clinical trial. *JAMA Surg*. 2021;156:137-46.
- Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. *Int J Obes*. 2008;32:1431-7.
- Agha M, Agha R. The rising prevalence of obesity: part A: impact on public health. *Int J Surg Oncol (N Y)*. 2017;2:e17.
- Kolotkin RL, Andersen JR. A systematic review of reviews: exploring the relationship between obesity, weight loss and health-related quality of life. *Clin Obes*. 2017;7:273-89.
- Brethauer SA, Kim J, el Chaar M, Papasavas P, Eisenberg D, Rogers A, et al. Standardized outcomes reporting in metabolic and bariatric surgery. *Surg Obes Relat Dis*. 2015;11:489-506.
- Blüher M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol*. 2019;15:288-98.
- Han Y, Jia Y, Wang H, Cao L, Zhao Y. Comparative analysis of weight loss and resolution of comorbidities between laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass: a systematic review and meta-analysis based on 18 studies. *Int J Surg*. 2020;76:101-10.
- Howard R, Chao GF, Yang J, Thumma J, Chhabra K, Arterburn DE, et al. Comparative safety of sleeve gastrectomy and gastric bypass up to 5 years after surgery in patients with severe obesity. *JAMA Surg*. 2021;156:1160-9.
- Courcoulas A, Coley RY, Clark JM, McBride CL, Cirelli E, McTigue K, et al. Interventions and operations 5 years after bariatric surgery in a cohort from the US National Patient-Centered Clinical Research Network Bariatric Study. *JAMA Surg*. 2020;155:194-204.
- Adams TD, Davidson LE, Litwin SE, Kim J, Kolotkin RL, Nanjee MN, et al. Weight and metabolic outcomes 12 years after gastric bypass. *N Engl J Med*. 2017;377:1143-55.
- Hu Z, Sun J, Li R, Wang Z, Ding H, Zhu T, et al. A comprehensive comparison of LRYGB and LSG in obese patients including the effects on QoL, comorbidities, weight loss, and complications: a systematic review and meta-analysis. *Obes Surg*. 2020;30:819-27.
- Helmiö M, Victorzon M, Ovaska J, Leivonen M, Juuti A, Peromaa-Haavisto P, et al. Comparison of short-term outcome of laparoscopic sleeve gastrectomy and gastric bypass in the treatment of morbid obesity: a prospective randomized controlled multicenter SLEEVEPASS study with 6-month follow-up. *Scand J Surg*. 2014;103:175-81.
- Hachem A, Brennan L. Quality of life outcomes of bariatric surgery: a systematic review. *Obes Surg*. 2016;26:395-409.
- Cooiman MI, Aarts EO, Janssen IMC, Hazebroek EJ, Berends FJ. Weight loss, remission of comorbidities, and quality of life after bariatric surgery in young adult patients. *Obes Surg*. 2019;29:1851-7.
- Dawani S, Dawani A, Ahmed H, Rasul S. Effectiveness of metabolic weight loss surgery on type-II diabetes, hypertension and lipid disturbances: review of systemic analysis. *Pak J Surg*. 2018;34:84-8.



# Finite element analysis evaluation of hypothetical alternative treatment scenarios for neglected developmental dysplasia of the hip

*Evaluación mediante análisis de elementos finitos de escenarios hipotéticos de tratamiento alternativo para la displasia del desarrollo de cadera desatendida*

Victor M. Araujo-Monsalvo<sup>1,2</sup>, Marcos Martínez-Cruz<sup>3</sup>, Lázaro Morales-Acosta<sup>3</sup>, Víctor M. Domínguez-Hernández<sup>1,2\*</sup>, Ramiro Cuevas-Olivo<sup>4</sup>, Jesus A. Carrillo-Pelaes<sup>3</sup>, Javier Perez-Orive<sup>3,5</sup>, and Elisa Martínez-Coria<sup>6</sup>

<sup>1</sup>Laboratorio de Biomecánica, Instituto Nacional de Rehabilitación "Luis Guillermo Ibarra Ibarra"; <sup>2</sup>Laboratorio Nacional Conahcyt en Biomecánica del Cuerpo Humano (LNC BiomeCH); <sup>3</sup>Facultad de Ingeniería, Universidad Nacional Autónoma de México; <sup>4</sup>Servicio de Ortopedia Pediátrica, Instituto Nacional de Rehabilitación "Luis Guillermo Ibarra Ibarra"; <sup>5</sup>Servicio de Neurociencias Básicas, Instituto Nacional de Rehabilitación "Luis Guillermo Ibarra Ibarra"; <sup>6</sup>Servicio de Tomografía Computada, Instituto Nacional de Rehabilitación "Luis Guillermo Ibarra Ibarra". Mexico City, Mexico

## Abstract

**Objective:** The study aimed to evaluate three different degrees of correction in the surgical treatment of neglected developmental dysplasia of the hip (DDH) using finite element models based on computed tomography. **Method:** Three tridimensional FEA models of hypothetical post-operative (PO) outcomes were developed, based on three tridimensional CT of a pediatric patient diagnosed with luxated neglected DDH: One with the acetabular index of the contralateral hip (CLAT); another based on a theoretical Bombelli biomechanical model (BMB); and another recreating the patient's actual PO. **Results:** The stresses in the affected hip were greater than those in the unaffected hip. CLAT showed the greatest stress and the smallest loading zone (LZ). In contrast, BMB showed the smallest stress and the biggest LZs. **Conclusions:** The approach based on the BMB gave the best results in terms of the distribution of the stresses over the hip, whereas the worst was CLAT. Qualitatively, estimating the stability and range of movement of the hip, the PO case was considered the best.

**Keywords:** Neglected developmental dysplasia of the hip. Dega acetabuloplasty. Finite element analysis. Biomechanics.

## Resumen

**Objetivo:** Evaluar tres diferentes grados de corrección en el tratamiento quirúrgico de la displasia del desarrollo de la cadera (DDH) inveterada mediante modelos de elementos finitos basados en tomografía computarizada. **Método:** Se desarrollaron tres modelos tridimensionales de elementos finitos de resultados posoperatorios hipotéticos, basados en tres tomografías computarizadas tridimensionales de un paciente pediátrico diagnosticado de displasia del desarrollo de la cadera luxada inveterada: uno con el índice acetabular de la cadera contralateral (CLAT), otro basado en un modelo biomecánico teórico de Bombelli (BMB) y otro recreando el posoperatorio real (PO) del paciente. **Resultados:** Los esfuerzos en la cadera afectada fueron mayores que en la cadera no afectada. El CLAT mostró el mayor esfuerzo y la menor zona de carga. Por el contrario, el BMB mostró el menor esfuerzo y las mayores zonas de carga. **Conclusiones:** La propuesta basada en el BMB dio los

### \*Correspondence:

Víctor M. Domínguez-Hernández

E-mail: vm\_dominguez@yahoo.com.mx

2444-0507/© 2023 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Date of reception: 13-03-2023

Date of acceptance: 26-10-2023

DOI: 10.24875/CIRUE.M23000742

Cir Cir (Eng). 2024;92(5):576-581

Contents available at PubMed

[www.cirugiaycirujanos.com](http://www.cirugiaycirujanos.com)

*mejores resultados en cuanto a la distribución de los esfuerzos sobre la cadera, mientras que la peor fue el CLAT. Cualitativamente, estimando la estabilidad y la amplitud de movimiento de la cadera, el caso PO se consideró el mejor.*

**Palabras clave:** *Dysplasia del desarrollo de la cadera inveterada. Acetabuloplastia tipo Dega. Análisis por elementos finitos. Biomecánica.*

## Introduction

Developmental dysplasia of the hip (DDH) is one of the main afflictions in pediatric orthopedics and a common cause of disability<sup>1,2</sup>. Diagnosis and treatment during the first 9 months of age generally result in a very positive prognosis<sup>3</sup>.

Neglected cases are those in which the condition has remained undiagnosed and untreated for a very long time, even years, which unfortunately is still prevalent in mid- and low-income countries. In such cases, the severity of the dysplasia is greater, the treatment is more aggressive, and the outcome is less predictable<sup>4</sup>. The consequences of neglected DDH include early joint degeneration during adulthood<sup>5,6</sup>. The relationship between clinical and biomechanical parameters is currently being investigated to predict the long-term performance of a DDH-affected hip<sup>7-10</sup>.

Neglected DDH is treated with open reduction, pelvic, and femoral osteotomies to correct the characteristic deformities of the condition (complete luxation, shallow and steep acetabulum, femoral anteversion, and valgus) and to restore congruence and function to the joint. For a better outcome, the hip should be reduced and well-oriented with conservative treatment before the surgical procedure, but in neglected cases, the surgeon cannot wait for this pre-requisite, so the reduction and reorientation are carried out in a single surgical procedure. Pediatric pelvic osteotomies represent one of the most technically challenging surgeries. Despite this difficulty, on many occasions, the surgical planning and clinical follow-up are carried out using plain radiographies (RX), due to its low cost and radiation dose, compared to other types of imaging studies, such as computed tomography (CT)<sup>3,11,12</sup>.

However, as some adult and older children hip dysplasia studies have shown<sup>7,13</sup>, the 3D models built from CT images, and its integration with biomechanical finite element analysis (FEA), make this technology a better alternative to conventional RX for the study, planning, and evaluation of treatment of the dysplastic hip, regardless of the increased cost and radiation dose<sup>3,12</sup>. Although the majority of examples in the literature are about adult dysplasia, the treatment for

pediatric neglected DDH patients could also benefit from the CT capacities for visualization and FEA integration.

Surgical planning assistance by means of biomechanical models could improve the neglected DDH treatment effectiveness, because it could allow predicting the behavior of the hip under different possible osteotomy approaches, each leading to a distinct post-operative (PO) outcome, and then choosing the scenario that offers the best biomechanical performance.

There exist different criteria for the ideal approach to dysplastic hip treatment. One criterion establishes as a PO goal an acetabular index (AI) value normal for the patient's age; for a unilateral DDH case, the contralateral control hip should have such a normal AI value (CLAT approach). In contrast, another criterion establishes that, for a unilateral, completely dislocated DDH case, the best option is to produce a configuration that avoids a re-dislocation, even if that implies an over-correction, this option corresponds to the real post-operative outcome with the patient (PO)<sup>4</sup>. A third criterion developed by Bombelli and based on 2D biomechanical models, suggested that the best hip joint configuration is one that has a horizontal loading zone (LZ) in the acetabular roof, right above the femoral head (Bombelli biomechanical model [BMB])<sup>14</sup>. Each of these criteria is optimized by following each of the three different approaches (CLAT, PO, and BMB, respectively).

The objective of this study is to develop CT-based biomechanical finite element models from a single patient to determine which osteotomy approach, each optimizing one of the aforementioned criteria, is the one that produces the best outcome, in terms of the mechanical stresses and LZs over the joint surfaces, as well as how this relates with clinical practice.

## Methods

This research work was approved by the research committee of our institute. The patient's parents signed the informed consent form.

The modeling was based on a 6-year-old female patient, diagnosed with unilateral neglected luxated

DDH on the right hip, and with no record of previous treatment. The contralateral hip was considered the control and the dislocated one was the case. A CT scan (LighSpeed® VCT 64, General Electric, Fairfield, CT, USA) of the patient was obtained with 0.625 mm slices from the vertebral body of L5 to the proximal third section of the femur. The modeling was based on this CT scan, and institutional guidelines for patient data protection and privacy were followed. The patient presented a complete hip dislocation and hip dysplasia grade IV for the DDH IHDI classification<sup>15</sup>, with AI values of 43° and 28° on the affected and non-affected side, respectively, as well as severe deformity of the acetabulum and proximal femur. One month after the CT scan, the patient was treated with one-stage open reduction and a Dega acetabuloplasty, and a derotational and shortening femoral osteotomy, postoperatively immobilized with a fiberglass pelvic cast for 12 weeks and then managed with physical therapy and rehabilitation for a further 12 weeks. Diagnosis, CT scan, and treatment were performed in our institution following standard clinical practice.

3D models of the pelvis and femur were built after the segmentation of the CT images. Posteriorly, those 3D models were used to generate tetrahedral meshes. Segmentation and reconstruction of the models were done using the InVesalius 3.1.1 (CTI Renato Archer, Campinas, SP, Brazil) and Autodesk Meshmixer (Autodesk, Inc., San Rafael, CA, USA).

Three hypothetical models were generated: CLAT, with the same AI value (28°) that in the contralateral hip; BMB, with an AI value of 0°, based on the theoretical model of Bombelli; and PO, that reproduces the post-operative outcome (AI = 7°), based on an AP RX projection taken at the end of the surgery (Fig. 1).

Since the starting position was a complete dislocation, the femur 3D model was translated and rotated to simulate the femoral derotational and shortening osteotomy. In all the scenarios, the inter-articular space was set to be the same as the one measured in the unaffected hip.

To transmit the loads during the FEA, similarly to the articular cartilage in the actual joints, interface volumes between the articular surfaces were generated. The generated meshes were composed of around 270,000 ten-noded tetrahedral elements (TET10). FEA was performed using ANSYS Mechanical APDL v14.5 (ANSYS Inc., Canonsburg, PA, USA).

All bones and interface volumes were considered to be linear elastic homogeneous isotropic solids, described by these mechanical properties: 17,000 MPa

and 0.3 for the elastic modulus and Poisson coefficient of the bone, respectively; and 15 MPa and 0.45 for the elastic modulus and Poisson coefficient of the cartilage, respectively<sup>13</sup>.

The finite element model was linear static, simulating a biped stance, applying the following loading conditions: 56% of the patient's body weight, in the vertical direction, over the S1 superior vertebral body surface, representing the body weight above the waistline; 63% of the patient's body weight over the greater trochanter and ilium wing (insertion zones of the abductor muscles), with force directions resembling the abductor muscle fibers; total movement restriction in the distal end of the proximal femur; rotational restriction on the pelvic bone. Loading conditions were formulated as previously described by other researchers<sup>13,16</sup>.

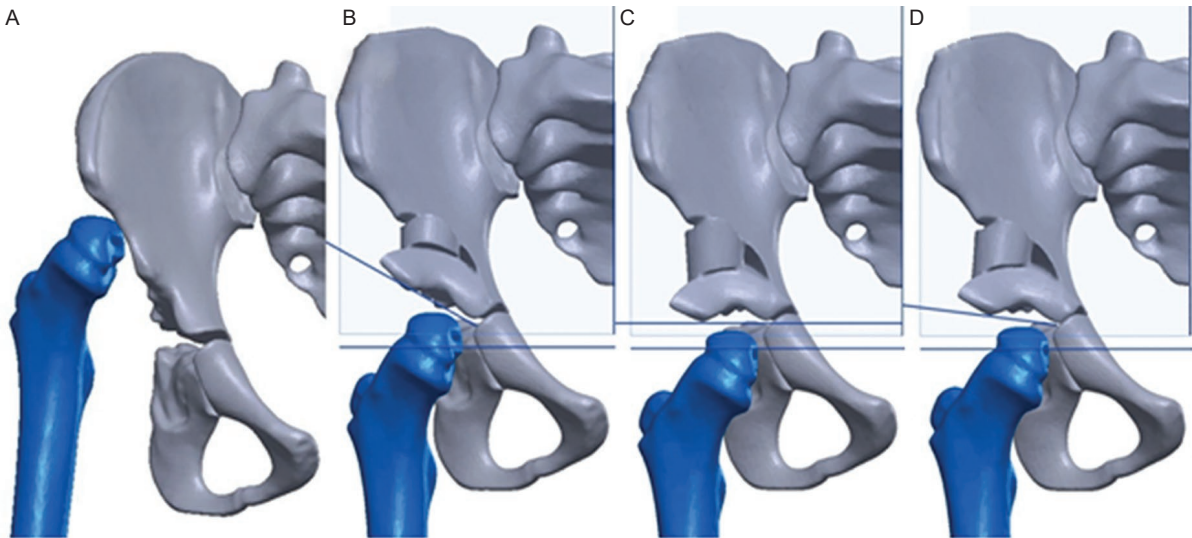
Maximum von Mises stresses (SMAX) and LZs over the articular surfaces of the acetabular roofs were registered. A LZ was arbitrarily defined as that in which the top 20% of the stresses were concentrated. For clarity, the LZ is presented as a percentage of the total articular surface. Quantitative and qualitative comparisons of the stress distributions in the acetabular roofs were made. As is standard practice, we considered that the lesser the SMAX the better, and the greater the LZ the better. The qualitative assessment involved the evaluation of joint congruency, location of stress peak values and bone protuberances, and an impression of dislocation risk by the medical team.

## Results

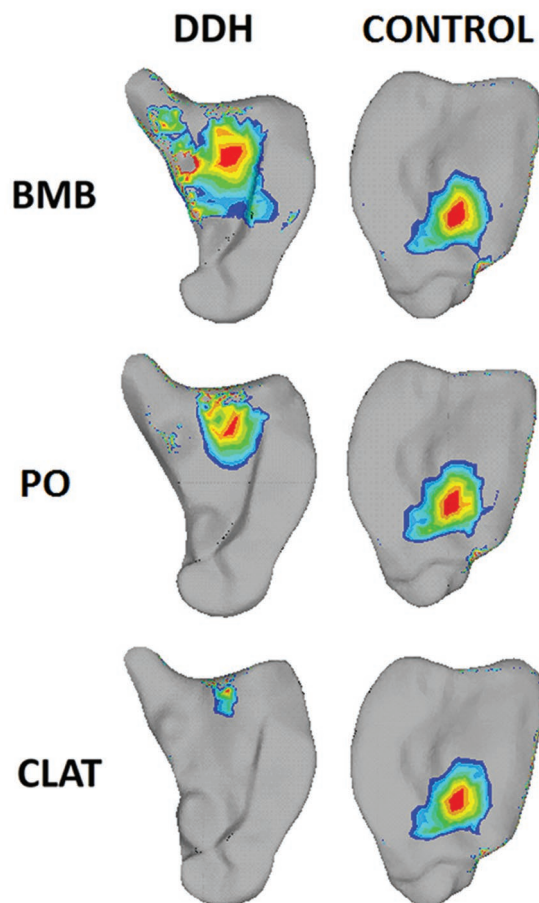
In the three analyzed alternatives, the stresses in the affected hip were greater than those in the unaffected hip. Stress magnitude and distribution in the control hip (SMAX of 30.3 MPa, and LZ of 20.7% of the total articular surface in the acetabular roof) did not seem affected by the configuration of the affected osteotomy-treated hip. Stress magnitude and distribution in the affected hip, however, did change considerably between scenarios (Fig. 2).

CLAT showed the greatest SMAX, 65.45 MPa, and an LZ of 9.9%, the smallest found (Figs. 3 and 4). Qualitatively, the instability of the setup and the disposition to redislocation were noticeable. Furthermore, the stresses are concentrated on the anterior flank, thereby increasing the risk of arthrosis.

In contrast, BMB showed the smallest SMAX of the affected hips, 33.99 MPa, and the biggest LZ, 62.7%. However, this scenario also showed a clear



**Figure 1.** CT 3D models of the neglected developmental dysplasia of the hip-affected hip. **A:** pre-operative state showing an IHD grade IV dysplasia. **B:** CLAT with acetabular index (AI) = 28°. **C:** bombelli biomechanical model scenario with AI = 0°. **D:** PO with AI = 7°.



**Figure 2.** Inferior view of the acetabular roofs showing loading zones on the simulated surgery analyzed both on control and affected hips. The scale was adjusted to show only the zones with von Mises stresses greater or equal to 80% of the maximum of each case.

over-correction and limb shortening. On the contrary, it shows the best load distribution by concentrating the stresses in the central portion.

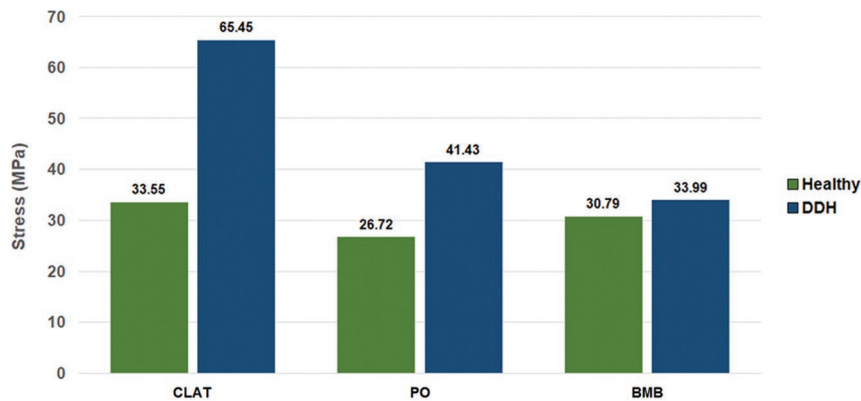
PO, a SMAX of 41.43 MPa and a LZ of 36% were found. It showed an apparent over-correction as well. In addition, the leading edge is tilted forward, which exerts excessive pressure on the femoral head.

## Discussion

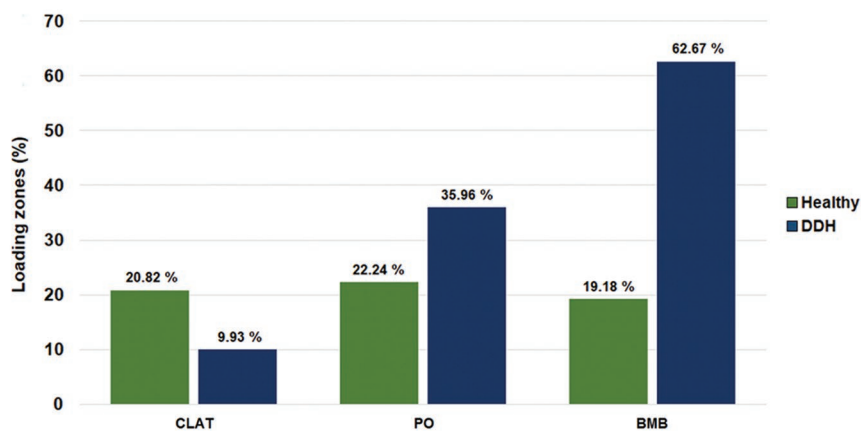
Based on our results, CLAT is the worst of the alternatives given that it showed considerable stress concentration on the articular surface and setup instability. Those characteristics, in an actual hip joint, are related to immediate post-operative complications, such as avascular necrosis and re-dislocations<sup>4,13,14</sup>.

Findings in CLAT also suggest that the AI, used on its own to evaluate a DDH-affected hip, could lead to an overestimation of the actual joint state. The AI offers only a measure of the steepness of the acetabular roof, and indirectly, assuming normal morphology, a measure of acetabular coverage or stability. Auxiliary radiological measurements, such as the Center-Edge or Wiberg angle, could help obtain a better estimate of acetabular coverage with RX images. Nevertheless, being plane projection measurements, it would be difficult to evaluate acetabular concavity, a determining characteristic of hip stability. Concavity is one of the most important reasons why the unaffected hip can be stable whereas the affected hip in the CLAT scenario is not, even if both hips have the same AI.





**Figure 3.** Maximum stresses in the acetabular roof of control and developmental dysplasia of the hip affected hips, in the surgical simulation scenarios.



**Figure 4.** Loading zones in the acetabular roof of control and developmental dysplasia of the hip affected hips, in terms of percentage of the total articular surface, on the surgical simulation scenarios.

When comparing BMB and PO, it is clear that the quantitative results of BMB are better than those of PO, as suggested by Bombelli's theoretical point of view, both in terms of maximum stresses and in terms of LZs. Qualitatively, it can be seen that the results also favor BMB, given that the load is concentrated in the central region of the hip with DDH, as opposed to PO which locates the LZs at the anterior border, with the risk of redislocation. However, the overcorrection observed in BMB could have adverse consequences for the function of the hip joint, since its range of motion would be limited, producing a discrepancy in the length of the limb and possibly an impingement.

A limitation of this study is that the models do not consider the effect of bone remodeling. In an actual patient, the hip is immobilized for at least 3 months after surgery, before being allowed to be loaded with

the body weight, and only then, the bone remodeling process is mechanically stimulated. Bone remodeling and resorption could generate concavity in shallow acetabular roofs and reduce bone protuberances that limit movement. It would be beneficial to perform a rigorous PO follow-up of neglected DDH patients to find out how the correction level achieved in the surgery and the bone remodeling relate to hip joint evolution in the short, medium, and long terms. Neglected DDH produces deformities that make each case unique, and so, it makes its treatment unique as well. Subsequent studies analogous to this one exploring additional patients would offer additional data.

The use of models similar to the ones used in this study could help achieve an optimal correction degree that maximizes stress distribution on joint surfaces and minimizes over-correction and its

consequences. Clinical implementation of such models could improve treatment effectiveness and patient life quality, and potentially delay or avoid adulthood DDH sequelae.

In conclusion, even though obtained biomechanical results seem to indicate that a hip would have a better stress distribution as the acetabular roof gets more horizontal, the morphologic characteristics of the hip should not be dismissed, as these factors could indicate overcorrections and its harmful consequences: impingement, limb length discrepancy, and limited range of movement.

Caution must be taken when using the AI to plan and evaluate treatment for neglected DDH; if auxiliary measurements and images, such as the Center-Edge angle or 3D visualizations, were not to be available or used to assess acetabular coverage and joint congruency, the sole AI value could be overestimating the actual state of the hip joint.

More studies are needed to determine the ideal correction degree for the surgical treatment of neglected DDH, to work out the best means to reproduce virtual surgery scenarios in the actual surgery, and to investigate the long-term consequences of the treatment and its planning procedures.

## Acknowledgments

The authors gratefully acknowledge the work done by technician Martín Luna Méndez from the CT and Ultrasound Department, at the Instituto Nacional de Rehabilitación “Luis Guillermo Ibarra Ibarra”.

## Funding

There were no funding sources.

## Conflicts of interest

The authors declare no conflicts of interest related to the present manuscript.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in

accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

## References

- Weinstein SL, Mubarak SJ, Wenger DR. Developmental hip dysplasia and dislocation: part I. Instr Course Lect. 2004;53:523-30.
- Dezateux C, Rosendahl K. Developmental dysplasia of the hip. Lancet. 2007;369:1541-52.
- Grissom L, Harcke HT, Thacker M. Imaging in the surgical management of developmental dislocation of the hip. Clin Orthop Relat Res. 2008;466:791-801.
- El-Tayeb HM. One-stage hip reconstruction in late neglected developmental dysplasia of the hip presenting in children above 8 years of age. J Child Orthop. 2009;3:11-20.
- Terjesen T. Residual hip dysplasia as a risk factor for osteoarthritis in 45 years follow-up of late-detected hip dislocation. J Child Orthop. 2011;5:425-31.
- Alcobá Díaz B, Luque Pérez R, García Bullón I, Moro Rodríguez LE, López-Durán Stern L. Long-term clinical and radiological outcomes in a series of 26 cases of symptomatic adult developmental dysplasia of the hip managed with Bernese periacetabular osteotomy. Rev Esp Cir Ortop Traumatol. 2015;59:421-8.
- Wang X, Peng J, Li D, Zhang L, Wang H, Jiang L, et al. Does the optimal position of the acetabular fragment should be within the radiological normal range for all developmental dysplasia of the hip? A patient-specific finite element analysis. J Orthop Surg Res. 2016;11:109.
- Lee KJ, Park SJ, Lee SJ, Naito M, Kwon SY. Biomechanical study on the efficacy of the periacetabular osteotomy using patient-specific finite element analysis. Int J Precis Eng Manuf. 2015;16:823-9.
- Ike H, Inaba Y, Kobayashi N, Yukizawa Y, Hirata Y, Tomioka M, et al. Effects of rotational acetabular osteotomy on the mechanical stress within the hip joint in patients with developmental dysplasia of the hip: a subject-specific finite element analysis. Bone Joint J. 2015;97-B:492-7.
- Huayamave V, Rose C, Serra S, Jones B, Divo E, Moslehy F, et al. A patient-specific model of the biomechanics of hip reduction for neonatal developmental dysplasia of the hip: investigation of strategies for low to severe grades of developmental dysplasia of the hip. J Biomech. 2015;48:2026-33.
- Clohisy JC, Carlisle JC, Trousdale R, Kim YJ, Beaulé PE, Morgan P, et al. Radiographic evaluation of the hip has limited reliability. Clin Orthop Relat Res. 2009;467:666-75.
- Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet. 2012;380:499-505.
- Zhao X, Yan YB, Cao PC, Ma YS, Wu ZX, Zhang Y, et al. Surgical results of developmental dysplasia of the hip in older children based on using three-dimensional computed tomography. Surg Res. 2014;189:268-73.
- Bombelli R. Osteoarthritis of the Hip. Berlin: Springer-Verlag; 1983.
- Narayanan U, Mulpuri K, Sankar WN, Clarke NM, Hosalkar H, Price CT, et al. Reliability of a new radiographic classification for developmental dysplasia of the hip. J Pediatr Orthop. 2015;35:478-84.
- De Leva P. Adjustments to zatsiorsky-seluyanov's segment inertia parameters. J Biomech. 1996;29:1223-30.

# Table of life for beneficiaries of the Institute of Security and Social Services of State Workers (ISSSTE), Mexico 2021

*Tabla de vida para derechohabientes del Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE), México 2021*

Judith E. García-de-Alba-Verduzco<sup>1</sup>, Javier E. García-de-Alba-Verduzco<sup>2</sup>, Ramiro López-Elizalde<sup>1</sup>, and Javier E. García-de-Alba-García<sup>3\*</sup>

<sup>1</sup>Subdirección Médica, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Ciudad de México; <sup>2</sup>Centro Universitario de Ciencias Biológicas, Universidad de Guadalajara, Guadalajara, Jalisco; <sup>3</sup>Cátedra García de Alba-Salcedo, Zapopan, Jalisco. Mexico

## Abstract

**Objective:** Determine the life expectancy in the covered population of the Institute of Security and Social Services of State Workers in México for 2021. **Method:** We used the abrogated method from Reed-Merrel, for calculate the life expectancy in age groups. **Results:** By 2021, life expectancy general was 79.51 years; 81.40 years and 78.91 years for woman and men, respectively. **Conclusions:** The calculated life expectancy not show a reduction in the population of federal and State employees in Mexico.

**Keywords:** Life expectancy. ISSSTE. Mexico.

## Resumen

**Objetivo:** Determinar la esperanza de vida en la población amparada del Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado en México para 2021. **Método:** Se utilizó el método abreviado de Reed-Merrel para calcular la esperanza de vida en grupos quinquenales de edad. **Resultados:** Para 2021, la esperanza de vida general fue de 79.51 años; de 81.40 años y 78.91 años para mujeres y para hombres, respectivamente. **Conclusiones:** La esperanza de vida calculada no presentó reducción después de la pandemia de COVID-19 para la población de empleados federales de México en 2021.

**Palabras clave:** Esperanza de vida. ISSSTE. México.

### \*Correspondence:

Javier E. García-de-Alba-García

E-mail: javiereduardogarciadealba@gmail.com

2444-0507/© 2023 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Date of reception: 21-06-2023

Date of acceptance: 26-10-2023

DOI: 10.24875/CIRUE.M23000743

Cir Cir (Eng). 2024;92(5):582-589

Contents available at PubMed

[www.cirugiaycirujanos.com](http://www.cirugiaycirujanos.com)

## Introduction

### Historical context

Two historical milestones in biostatistics and epidemiology provide the foundation for life tables.

The first milestone is the pioneering work published in 1662 by Captain John Graunt, titled *Natural and Political Observations Mentioned in a Following Index, and Made Upon the Bills of Mortality*. This work laid the groundwork for calculating mortality rates as we know them today (deaths within a population over a period of time/population at the midpoint of that period) by a population constant (of 100, 1000, or 10,000 inhabitants) for that time and place. Graunt's work was based on weekly parish records of deaths and baptisms in London, a system established due to the bubonic plague epidemic in England.

Deaths were only estimated generically, indicating place and time, e.g., "Smallpox arrived in New Spain via the port of Veracruz in the spring or summer of 1779, spreading along the roads between the towns leading to Puebla and Mexico City, which was reached in autumn 1779. At least 45,000 cases were recorded in the last quarter of the year, with more than 14,000 fatalities. From Mexico City, it spread westward, reaching Toluca in December, Michoacán in early 1780, and New Galicia by February, affecting Guadalajara, where 1,268 inhabitants died between March and May<sup>1</sup>."

The second milestone, mathematically driven by European mercantilist development, was achieved by Edmund Halley (with support from Gottfried Leibniz and endorsement by the Royal Society of England), who studied birth and death records from Breslau (a city in southwestern Poland) between 1687 and 1691. His findings were published in 1693 in one of Europe's earliest scientific journals, *Philosophical Transactions*, under the title *An Estimate of the Degrees of Mortality of Mankind, Drawn from Curious Tables of the Births and Funerals at the City of Breslaw; with an Attempt to Ascertain the Price of Annuities upon Lives*, aimed undoubtedly at insurance companies to help them calculate premium values and annuity payments based on age<sup>2</sup>. The evolution of life table calculations has transitioned from the private domain (economic risk assessment) to the public sphere (health assessment) and from manual tabulation in so-called "statistical sheets" to computerized programs like Epidat, developed and freely distributed

by the Pan American Health Organization and the Health Council of the Regional Government of Galicia (Spain)<sup>3</sup>. Life tables are now a commonly used tool, and their application reveals that among the nations of the world, Japanese women currently have the highest life expectancy at birth, surpassing 87 years. However, it is worth noting that over 120 years ago, in 1840, the record was held by Swedish women, with an estimated life expectancy of 46 years<sup>4</sup>.

### Applied context

Life tables have extended the narrow measure of early-life mortality to capture a population's life course, indicating the average death age within that population, thus making life expectancy a crucial indicator of population health. In the pre-modern world of 1800, life expectancy hovered around 30 years; today, no country has such a low life expectancy. Despite nearly tripling global life expectancy, inequality remains significant; for example, prior to the pandemic in 2019, the Central African Republic had a life expectancy of 53 years, while Japan's was 30 years higher<sup>5</sup>.

### Technical background

A life table is a methodological statistical construct used to analyze survival probability within a specific population in a given time-space environment, considering interactions with epidemiological agents influencing health and disease processes at the group level. The life table also functions as a biostatistical measure of premature mortality within a population, representing the average age of death in the group, with survival results significantly affected by infant and preschool mortality rates.

There are 2 main types of life tables:

- Static period tables: Show current year-by-year or age-grouped probability of death.
- Cohort tables: Show death probability for individuals within a specific cohort (e.g., year of birth) over their lifetime.

By age grouping, life tables can take 2 forms:

- Year-by-year tables: From birth to the last known age.
- Abbreviated tables: Age values in the life table are presented in groups rather than individually, typically organized by functional life stages, such as under 1 year, ages 1–4, ages 5–9, and so forth in five-year increments up to 85+ years.



In this study, we use static life tables, applying Reed and Merrell's abbreviated method, as published in the *American Journal of Hygiene* (now the *American Journal of Epidemiology*) by the Department of Biometrics and Vital Statistics at Johns Hopkins University in 1939<sup>6</sup>.

The tables were applied to individuals covered by the Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE), comprising employees and family members of federal departments forming the operational apparatus of the federal government<sup>7</sup>.

## Objective

This report aims to estimate the life expectancy of the second-largest population of public servants in the country served by ISSSTE and their beneficiaries in 2021.

## Method

The study population included those covered by ISSSTE as recorded in the *ISSSTE Yearbook* for 2021<sup>7</sup> and deaths recorded for ISSSTE beneficiaries in 2021, included in the dynamic database of the Ministry of Health<sup>8</sup>.

Data were grouped into five-year age intervals, except for populations under 1 year (infants), 1-4 years (preschool), and 85+ years (elderly)<sup>9</sup>.

Life expectancy was calculated following Reed and Merrell's abbreviated method<sup>6</sup> and recommendations by Camel for abbreviated life tables<sup>10</sup>.

## Results

The construction of a life table is labor-intensive and requires adherence to a set of specifications listed after the tables (Table 1) for each column, labeled with a letter of the alphabet at the top of each column.

Accordingly, we estimated a life expectancy of 79.51 years for the population of both sexes covered by ISSSTE in the country for the year 2021 (Table 2); 81.40 years for women and 78.91 years for men (Tables 3 and 4).

## Discussion

The results obtained in this study are valid for the life tables of the ISSSTE user population residing in Mexico in 2021. However, as with any population data

**Table 1. Specifications for the Construction of Life Tables**

---

(a) = Age groups
(b) = ISSSTE Population (2021 Yearbook)
(c) = Deaths registered (ISSSTE 2021 Yearbook)
(d) = cbbc
(e) = For age -1 year: $2d_2 + d_2 + d_{2d}$ ; For ages 1-4 years: $4 \times (2d_2 + d) \times (2 + d_{2d})$ ; For ages 5-9 to 80-84 years: $5 \times (2d_2 + d) \times (2 + d_{2d})$ ; For age 85 + years: 1.001.00
(f) = For age -1 year: 100,000100,000; For ages 1-4 years: $(e-1 \text{ year}) \times (f-1 \text{ year}) - (f-1 \text{ year})$ ; $(e-1 \text{ year}) \times (f-1 \text{ year}) - (f-1 \text{ year})$ ; For ages 5-14 years: $(e1-4 \text{ years}) \times (f1-4 \text{ years}) - (f1-4 \text{ years})$ ; $(e1-4 \text{ years}) \times (f1-4 \text{ years}) - (f1-4 \text{ years})$ , and so on
(g) = For all age groups: $(e) \times (f)(e) \times (f)$
(h) = For age -1 year: $(0.25) \times (f-1 \text{ year}) + (0.75) \times (f1-4)(0.25) \times (f-1 \text{ year}) + (0.75) \times (f1-4)$ ; For ages 1-4 years: $(1.9) \times (f1-4 \text{ years}) + (2.1)(1.9) \times (f1-4 \text{ years}) + (2.1)$ ; For ages 5-9 years: $(5) \times (f5-9 \text{ years}) + f10-14 \text{ years}2$ $(5) \times (f5-9 \text{ years}) + 2f10-14 \text{ years}$ ; Continue similarly up to ages 80-84 years: $(5) \times (f80-84 \text{ years}) + (5) \times (f85 + \text{years})$ $22(5) \times (f80-84 \text{ years}) + (5) \times (f85 + \text{years})$ ; For age 85 + years: $\log(85) \times (f85 + \text{years}) \log(85) \times (f85 + \text{years})$
(i) = For age 85 + years: $h85 + \text{yearsh}85 + \text{years}$ ; For age 80-84 years: $h80-84 \text{ years} + h75-79 \text{ yearsh}80-84 \text{ years} + h75-79 \text{ years}$ ; Continue in this pattern until age 1-4 years: $i5-9 \text{ years} + h1-4 \text{ yearsi}5-9 \text{ years} + h1-4 \text{ years}$ ; -For age -1 year: $i1-4 \text{ years} + h-1 \text{ yeari}1-4 \text{ years} + h-1 \text{ year}$
(j) = (i) of each age group/(f) of the same age group.

---

on birth and mortality, they may exhibit unquantified registration biases, limiting their generalization since the ISSSTE beneficiary status is sometimes not recorded for individuals born or deceased outside the institutional setting. This is not the case with hospital births and deaths, so we consider the table to be a reasonable approximation.

In our case, the total life expectancy calculated for both sexes was 79.51 years among ISSSTE users in Mexico in 2021, slightly lower than the life expectancy for ISSSTE in Jalisco in 2016, which was calculated at 80.81 years<sup>11</sup>.

The life expectancy estimated for ISSSTE is higher compared to the national life expectancy, which in 2018 was recorded at 75.0 years (72.2 years for men and 77.9 years for women) and in 2022 was 75.32 years (72.62 years for men and 78.38 years for women), with a slight increase influenced by the impact of the COVID-19 pandemic in the previous years<sup>12</sup>.

It is important to note that, in our setting, life expectancy has been increasing over time, a trend observed in several population groups, especially where there is social security coverage. For example, in the city of Guadalajara in 1974, the total life expectancy was 67.80 years<sup>13</sup>, and for the insured under the Mexican Social Security Institute (IMSS) in Jalisco in 1983, life expectancy for both sexes was 74.97 years (73.38 years

**Table 2. ISSSTE Life Tables 2021, Population of Both Sexes**

Age Groups (a)	Population (1) (b)	Deaths (2) (c)	Specific Rates (d)	Adjusted Probability (e)	Standard Population (f)	Theoretical Deaths (g)	Survival Years at Midpoint (h)	Remaining Life Years (i)	Life Expectancy (j)
< 1 year	67,440	304	0.0045077	0.00449756	100,000	450	99,662	7,951,991	79.51
1-4 years	327,779	67	0.0002044	0.0008175	99,550	81	398,029	7,852,329	78.87
5-9 years	754,782	64	0.0000847	0.00042348	99,469	42	497,240	7,454,300	74.94
10-14 years	913,205	74	0.0000810	0.00040498	99,427	40	497,035	6,957,060	69.97
15-19 years	931,580	177	0.0001899	0.0009494	99,387	94	496,700	6,460,025	64.99
20-24 years	613,784	184	0.0002997	0.00149827	99,293	149	496,092	5,963,325	60.05
25-29 years	565,326	273	0.0004829	0.00241391	99,144	239	495,122	5,467,233	55.14
30-34 years	663,840	594	0.0008947	0.004471499	98,905	442	493,420	4,972,111	50.27
35-39 years	822,005	925	0.0011252	0.00562283	98,463	553	490,932	4,478,691	45.48
40-44 years	843,293	1462	0.0017333	0.00865899	97,910	847	487,743	3,987,759	40.72
45-49 years	881,095	2413	0.0027386	0.01367427	97,063	1327	481,997	3,500,016	36.05
50-54 years	918,255	3476	0.0037854	0.01889124	95,736	1808	474,160	3,018,019	31.52
55-59 years	1,067,404	6332	0.0059321	0.02957278	93,928	2778	462,695	2,543,859	27.08
60-64 years	1,108,627	8383	0.0075616	0.03766559	91,150	3433	447,167	2,081,164	22.83
65-69 years	936,458	9610	0.0126207	0.06270779	87,717	5500	424,835	1,633,997	18.62
70-74 years	726,816	10,225	0.0140682	0.06984967	82,217	5743	396,727	1,209,162	14.70
75-79 years	546,759	10,043	0.0183682	0.09100519	76,474	6959	364,972	812,435	10.62
80-84 years	405,867	9127	0.0224876	0.11187826	69,515	7729	328,252	447,463	6.43
85 + years	586,759	14,668	0.0249983	1.00000	61,786	61,786	119,211	119,211	1.92
No age	0	2	NC	NC	NC	NC			
Total	13,681,077	78,403	0.00573076						

(1) ISSSTE: Statistical Yearbooks 2021, Chapter 1, Population Statistics 1.4.

(b) Secretaría de Salud. DGIS. Cubos Dinámicos.

NC: Not Calculable

for men and 76.40 years for women)<sup>14</sup>. By 2015, the IMSS-insured population in Jalisco, covering 81% of the state's workforce<sup>15</sup>, recorded a total life expectancy of 79.22 years<sup>16</sup>. This progression aligns with the general increase in modern human life expectancy, driven by a demographic transition from high birth and death rates to a regime of low birth and death rates, where social security contributes to extending lifespan by saving lives and preventing deaths at early ages, allowing human populations to live longer and reach older ages of death, as seen in developed societies<sup>4</sup>.

This increase in age at death is both a product and a driver of social determinants that compel us to maintain positive life expectancy trends in the population,

in this case, by expanding coverage and reducing barriers to social security for its clear impact on life duration<sup>4</sup>, as populations lacking social security tend to accentuate and expose fundamental types of human inequality<sup>17</sup> (class, gender, ethnic, urban, etc.) throughout their life course, shortening or slowing down its length or varying the internal distribution of human life expectancy within the population structure—inequalities that have not been observed among non-human primates for millions of years<sup>4</sup>.

In the case of social security in Mexico (ISSSTE and IMSS), an operational trajectory of three-quarters of a century has been achieved, where advancing the survival frontier toward older ages and individual life expectancy shows fewer disparities, as reflected in our

Table 3. ISSSTE Life Tables 2021, National Female Population

Age Groups (a)	Population (1) (b)	Deaths (2) (c)	Specific Rates (d)	Adjusted Probability (e)	Standard Population (f)	Theoretical Deaths (g)	Survival Years at Midpoint (h)	Remaining Life Years (i)	Life Expectancy (j)
< 1 year	33,234	135	0.0040621	0.00405386	100,000	405	99,696	8,140,043	81.40
1-4 years	159,863	33	0.0002064	0.00082551	99,595	82	398,207	8,040,347	80.73
5-9 years	369,495	29	0.0000784	0.00039198	99,513	39	497,467	7,642,140	76.79
10-14 years	447,219	30	0.0000670	0.00033498	99,474	33	497,287	7,144,673	71.82
15-19 years	456,472	62	0.0001358	0.00067895	99,441	67	497,037	6,647,386	66.84
20-24 years	310,169	58	0.0001869	0.00093441	99,374	92	496,640	6,150,349	61.89
25-29 years	332,693	97	0.0002915	0.00145728	99,282	144	496,050	5,653,709	56.94
30-34 years	399,509	194	0.0004855	0.00242691	99,138	240	497,590	5,157,590	52.02
35-39 years	473,837	315	0.0006647	0.00332239	98,898	328	493,670	4,660,069	47.11
40-44 years	468,520	542	0.0011568	0.00578065	98,570	569	491,427	4,166,399	42.26
45-49 years	495,645	939	0.0018945	0.00946000	98,001	927	487,687	3,674,972	37.49
50-54 years	536,675	1418	0.0026421	0.01319307	97,074	1280	482,170	3,187,285	32.83
55-59 years	633,379	2707	0.0042739	0.02132393	95,794	2042	473,865	2,705,115	28.23
60-64 years	640,165	3545	0.0055376	0.02761154	93,752	2588	462,290	2,231,250	23.79
65-69 years	527,823	4191	0.0079401	0.03954351	91,164	3604	445,818	1,768,960	19.40
70-74 years	406,988	4455	0.0109462	0.05443308	87,560	4766	425,885	1,323,142	15.11
75-79 years	312,018	4580	0.0146786	0.07285827	82,794	6032	398,890	897,257	10.83
80-84 years	234,796	4680	0.0199321	0.0986770	76,762	7574	364,875	498,367	6.49
85 + years	333,157	8426	0.0252913	1.00000	69,188	69,188	133,492	133,492	1.92
No age	NA	2	NC						
Total	7,571,657	36,438	0.0048124						

(1) ISSSTE: Statistical Yearbooks 2021, Chapter 1, Population Statistics 1.4.

(b) Secretaría de Salud. DGIS. Cubos Dinámicos.

NA: Not Applicable; NC: Not Calculable

data, presenting an optimistic scenario. If the current pace of life expectancy progress continues, a good number of children born in this millennium could celebrate their 100<sup>th</sup> birthday.

However, the uncertainty linked to the persistence of inequality and inequity in our environment tempers this optimism, as in reality, life expectancy may increase only slightly, despite significant advancements in understanding how long humans have lived and how long they might live over the last three decades. Thus, achieving a more egalitarian population-level life expectancy depends on social, economic, health, cultural, and political actions to improve quality of life in longevity, requiring the development of more robust sociodemographic methods for forecasting and evaluating population vitality<sup>18</sup>.

Concerning methodology, Dowd and Hamoud<sup>19</sup> suggest that certain precautions can prevent biases in calculating life expectancy:

- Whenever possible, identify trends by tracking the same population.
- When comparing different populations, stratify the characteristics that have remained stable for at least one human generation, which do not significantly impact early life. This allows life expectancy measures to be calculated over time for subgroups, although this does not ensure valid interpretation of observed differences.
- Stratify populations with explicit reference to their social history, using a clear and articulated theoretical-conceptual framework in both social and biological sciences.

**Table 4. ISSSTE Life Tables 2021, National Male Population**

Age Groups (a)	Population (1) (b)	Deaths (2) (c)	Specific Rates (d)	Adjusted Probability (e)	Standard Population (f)	Theoretical Deaths (g)	Survival Years at Midpoint (h)	Remaining Life Years (i)	Life Expectancy (j)
< 1 year	34,206	169	0.0049406	0.004928425	100,000	494	99,629	7,891,349	78.91
1-4 years	167,916	34	0.0002024	0.000809518	99,506	20	397,982	7,791,720	78.30
5-9 years	385,287	35	0.0000908	0.000453979	99,486	45	497,317	7,393,738	74.31
10-14 years	465,986	44	0.0000944	0.000471978	99,441	46	497,090	6,896,421	69.35
15-19 years	475,108	115	0.0002420	0.001209854	99,395	120	496,675	6,399,331	64.38
20-24 years	303,618	126	0.0004149	0.00207407	99,275	205	495,862	5,902,656	59.45
25-29 years	232,633	176	0.0007565	0.00378107	99,070	374	494,415	5,406,794	54.57
30-34 years	264,331	400	0.0015132	0.00756028	98,696	746	491,615	4,912,379	49.77
35-39 years	348,168	610	0.0017520	0.00875233	97,950	857	487,607	4,420,764	45.13
40-44 years	374,773	920	0.0024548	0.01225895	97,093	1190	482,490	3,933,157	40.50
45-49 years	385,450	1474	0.0038241	0.01908401	95,903	1830	474,940	3,450,667	35.98
50-54 years	381,580	2058	0.0053933	0.02689397	94,073	2529	464,042	2,975,727	31.63
55-59 years	434,025	3625	0.0083520	0.04158633	91,544	3806	448,292	2,511,685	27.43
60-64 years	468,462	4838	0.0103274	0.05137173	87,773	4507	427,597	2,063,393	23.50
65-69 years	408,635	5419	0.0132612	0.06586936	83,266	5484	401,620	1,635,796	19.54
70-74 years	319,828	5770	0.0180408	0.08939759	77,382	6917	369,617	1,234,176	15.94
75-79 years	234,741	5463	0.0232724	0.11502356	70,465	8105	334,562	864,559	12.26
80-84 years	171,071	4447	0.0259950	0.12830732	63,360	8129	368,132	529,997	8.36
85 + years	253,602	6242	0.0246133	1.00000	83,893	83,893	161,865	161,865	1.92
Total	6,109,420	41,965	0.0068689						

(1) ISSSTE: Statistical Yearbooks 2021, Chapter 1, Population Statistics 1.4.

NA: Not Applicable; NC: Not Calculable

If a result is measured in non-comparable populations, the mere fact that measurements are calculated in two “circumstances” does not make the discrepancy a “trend,” and the irresponsible use of terms such as “decline” or “decrease” may do more harm than good for the public<sup>19</sup>.

In the qualitative dimension, varied results in life expectancy continue to be found. For example, we observed a gender difference, with a higher expectancy for women. This trend has been corroborated nationwide since the records of 1930, which showed a life expectancy for women of 34.7 years and 33.0 years for men; or the spatial variability seen in 2019, when life expectancy was highest in Mexico City (formerly the Federal District) at 76.5 years and in Baja California at 75.9 years, while the lowest was recorded in Guerrero at 73.2 years and in Oaxaca at 74.0 years<sup>12</sup>.

Other non-national examples show that life expectancy varies across populations, such as in the United States, where American Indian and Alaska Native populations have the lowest life expectancy of all populations in the nation and have seen reductions in their life expectancy indicators across most counties, with a gap exceeding 21 years<sup>20</sup>. In Spain, the total life expectancy increased by 1.17 years from 2010 to 2018, but this increase was not proportionate between men and women; it rose by 1.41 years for men and only by 0.82 years for women, reducing the relative difference in life expectancy between women and men by 0.5 years, although women continued to have a longer life expectancy by an absolute margin of 5.39 years in 2018<sup>21</sup>.

The complexity of life expectancy is apparent in the overall mortality rate (per 1000 inhabitants), which may show considerable variation due to greater population



aging, higher lethality from specific diseases, or declines in infant mortality rates (now leveling between boys and girls), and the social determinants that create significant contrasts between geographic areas, ethnic groups, and socioeconomic levels<sup>22</sup>, where poverty and poorer health indicators, linked to sub-standard housing, issues in accessing a healthy diet, unemployment, underemployment, poor working conditions with increased health risks, higher consumption of toxic substances (alcohol, tobacco, drugs), lower education levels, less healthy habits, and limited access to many health benefits, play a key role.

Regarding changes in life expectancy in ISSSTE based on 2016 data<sup>11</sup> and this presentation (2021), whose slight magnitude may be attributed to the COVID-19 epidemic, its sustainability can also be credited to the protection provided by social security. Although we believe that future increases will likely be smaller vs those seen for Guadalajara and IMSS in Jalisco in past decades<sup>13,14</sup>, paradoxically, these will result from the increased social security coverage and the balancing of mortality causes among the analyzed groups<sup>23</sup>, as well as the impact of new epidemic events due to increasing globalization affecting our country. This should not discount the existence or persistence of “intrapopulation archipelagos or pockets” that could affect the heterogeneous population of social security users, in this case, federal employees covered by ISSSTE.

Thus, the rise in institutional population longevity should prompt us to consider:

- Whether our healthy, disability-free life expectancy will truly increase as much as total life expectancy<sup>24</sup>.
- Whether these demographic changes are fundamentally quantitative, without changes in the social context of human longevity, i.e., without a true flourishing of humanity<sup>25</sup>.

## Conclusions

While a country's life expectancy increases with national income, it has also become evident that community-based policies and strategies are essential. These include equality and equity in access to goods and services, education (especially for women), gender empowerment, genuine community development associations, and population-wide political participation-not a model of mass consumption economy, limited social security, market-based health care, limited health promotion and protection, or inequalities related to gender, ethnicity, and age<sup>26</sup>.

Unfortunately, there are few national studies that evaluate inequalities in life expectancy or analyze these according to social, economic, and cultural dimensions, which would aid in developing tools focused on service unity, prevention, and a multidisciplinary approach to health-disease understood as a process, helping to reduce differentials.

It is thus noteworthy that having social security coverage promotes greater life expectancy (79.51 years among ISSSTE users in Mexico for 2021), making it urgent to advance in social security<sup>27</sup>, taking advantage of theoretical advances and evidence collected on the influence of social structure on the health of social groups. The study of life expectancy is still an emerging field, not yet clearly defined, and should not be conflated with the traditional risk factor approach<sup>28</sup>.

## Funding

None declared.

## Conflicts of interest

None declared.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

## References

1. Méndez Main S. Xalapa, Jilotepec y Naolinco: una ruta de contagio en el camino Veracruz-México, 1765-1820. En: Magaña-Mancilla MA, coordinador. Epidemias y rutas de propagación en la Nueva España y México (siglos XVIII y XIX). México: Universidad Autónoma de Baja California-Instituto de Investigaciones Culturales-Museo; 2013. p. 13-24.
2. Robles Villane A. Más allá de las estrellas: aportes de Edmond Halley a la demografía. *Otros Diálogos*. 2022;18. Disponible en: <https://otrosdialogos.colmex.mx/mas-alla-de-las-estrellas-aportes-de-edmond-halley-a-la-demografia>
3. Epidat 3.1. Consellería de Sanidade. SERGAS. Disponible en: [https://www.sergas.es/Saude-publica/Epidat-3-1-descargar-Epidat-3-1-\(espanol\)?idioma=es](https://www.sergas.es/Saude-publica/Epidat-3-1-descargar-Epidat-3-1-(espanol)?idioma=es)
4. Aburto JM. Dynamics of life expectancy and life span equality. *PNAS*. 2020;117:5250-9.
5. Roser M, Ortiz-Espina E, Ritchie H. Life expectancy. *Our World in Data*. 2013. (Consultado el 22-03-2022.) Disponible en: <https://ourworldindata.org/life-expectancy>

6. Reed LJ, Merrel MA. Short method for constructing and abridged life table. *The American Journal of Hygiene*. 1939;30:33-62.
7. Anuario Estadístico. ISSSTE. 2021. Disponible en: <http://www.issste.gob.mx/datosabiertos/anuarios/anuarios2021.html>.
8. Secretaría de Salud. Cubos dinámicos. Mortalidad. 2021. (Consultado el 22-03-2022.) Disponible en: [http://www.dgis.salud.gob.mx/contenidos/basesdedatos/bdc\\_defunciones\\_gobmx.html](http://www.dgis.salud.gob.mx/contenidos/basesdedatos/bdc_defunciones_gobmx.html)
9. García Pulgarín LV, García Ortiz LH. El adulto mayor maduro: condiciones actuales de vida. *Rev Med Risaralda*. 2005;11(2). (Consultado el 22-03-2022.) Disponible en: <https://revistas.utp.edu.co/index.php/revista-medica/article/view/1189>
10. Camel Vargas F. Estadísticas médicas y de salud pública. La Habana, Cuba: Unidad Andrés Boin; 1968. p. 371-81.
11. García de Alba García J.E, López Elizalde R, García de Alba Verduzco J.E. 2023. Tabla de Vida Abreviada, para la población amparada del ISSSTE-Jalisco. 2016, Salud Jalisco. En: Valdez Zepeda A, Salazar Estrada JG y Barragan Bautista E. Las tecnologías en y para la salud pública. Universidad de Guadalajara. CUSUR. México. pp 537-552.
12. CONAPO. La situación demográfica de México. (Consultado el 01-05-2023.) Disponible en: <http://www.gob.mx/conapo>
13. García de Alba García JE, Espinoza Hernández J, Morán González R. Tablas de vida para la ciudad de Guadalajara 1974-1975. *Salud Publica de México*. 2014;18:1005-9.
14. García de Alba García JE, Barba Marabel O. Tablas de vida para la población derechohabiente del Instituto Mexicano del Seguro Social, delegación estatal en Jalisco 1983. *Salud Publica de México*. 1976;27:155-160.
15. MIDE Jalisco. Monitoreo de indicadores del desarrollo de Jalisco. (Consultado el 12-05-2023.) Disponible en: <https://mide.jalisco.gob.mx>.
16. García de Alba García JE, Salcedo Rocha AL, Milke Najer ME, Reynoso C, García de Alba Verduzco JE, De Celis Carrillo R. Tablas de vida 2015, población usuaria del Instituto Mexicano del Seguro Social - Jalisco. *Revista Médica del IMSS*. 2018;56:261-73.
17. Olshansky J, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody J, et al. Potential decline in life expectancy in the United States in the 21<sup>st</sup> Century. *New Engl J Med*. 2005;352:1138-45.
18. Vaupel JW, Villavicencio F, Bergeron-Boucher MP. Demographic perspectives on the rise of longevity. *Proc Natl Acad Sci U S A*. 2021; 118:e2019536118.
19. Dowd JB, Hamoud A. Is life expectancy really falling for groups of low socio-economic status? Lagged selection bias and artefactual trends in mortality. *Int J Epidemiol*. 2014;43:983-8.
20. NIH: News Releases. Thursday, June 16, 2022: Life expectancy in the U.S. increased between 2000-2019, but widespread gaps among racial and ethnic groups exist. (Consultado el 21-03-2023.) Disponible en: <https://www.nih.gov/news-events/news-releases/life-expectancy-us-increased-between-2000-2019-widespread-gaps-among-racial-ethnic-groups-exist>
21. Carlos Sánchez y Sergio Fernández 2020 . En: Menor esperanza de vida en los grupos sociales con menos ingresos <https://www.consumidor.es,2020/08/13,menor-esp> (consultado el 18/06/2024).
22. Lustig N. Salud y desarrollo económico. El caso de México. *El Trimestre Econ*. 2007;74:793-822.
23. Heuveline P. Global and national declines in life expectancy: an end-of-2021 assessment. *Popul Dev Rev*. 2022;48:31-50.
24. Robine JM. Ageing populations: we are living longer lives, but are we healthier? UN DESA Publications. United Nations. (Consultado el 22-05-2022.) Disponible en: <https://desapublications.un.org/working-papers/ageing-populations-we-are-living-longer-lives-are-we-healthier>
25. Dieterlen P. Cuatro enfoques sobre la idea del florecimiento humano. *Desacatos*. 2007; (23):147-58.
26. Freeman T, Gesesew HA, Bamba C, Giugliani ERJ, Popay J, Sanders D, et al. Why do some countries do better or worse in life expectancy relative to income? An analysis of Brazil, Ethiopia, and the United States of America. *Int J Equity Health*. 2020;19:202.
27. Soria Romero Z, Montoya Arce BJ. Envejecimiento y factores asociados a la calidad de vida de los adultos mayores en el Estado de México. *Pap Poblac*. 2017;23:59-93.
28. Álvarez Castaño LS. Los determinantes sociales de la salud: más allá de los factores de riesgo. *Revista Gerencia y Políticas de Salud*. 2009; 8:69-79.

# Association of Vitamin D and magnesium levels with severity and mortality in patients with COVID-19

## Asociación de los niveles de vitamina D y magnesio con la gravedad y la mortalidad en pacientes con COVID-19

Mariela M. García-Zendejas<sup>1</sup>, Edgar A. Cano-Torres<sup>2</sup>, and Luis E. Simental-Mendía<sup>3\*</sup> 

<sup>1</sup>Servicio de Urgencias, Hospital General Salvador Zubirán Anchondo, Chihuahua, Chihuahua; <sup>2</sup>Department of Internal Medicine, Hospital Rebren, Durango, Durango; <sup>3</sup>Unidad de Investigación Biomédica, Delegación Durango, Instituto Mexicano del Seguro Social, Durango, Durango. México

### Abstract

**Objective:** The study aimed to determine the association between serum magnesium and Vitamin D levels with the severity and mortality by coronavirus disease 19 (COVID-19) in hospitalized patients. **Method:** Men and women over 18 years of age with probable COVID-19 were enrolled in a case-control study. Patients with a positive or negative test for Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were allocated into case or control groups, respectively. Vitamin D deficiency was defined by concentrations < 20 ng/mL and hypomagnesemia by serum levels < 1.8 mg/dL. **Results:** A total of 54 patients, 30 women and 24 men, were enrolled and allocated into the groups with (n = 27) and without (n = 27) COVID-19. The logistic regression analysis showed that Vitamin D deficiency (odds ratio [OR] = 6.13; 95% confidence intervals [CI]: 1.32-28.34) and insufficiency (OR = 0.12; 95% CI: 0.02-0.60) are significantly associated with hospitalization. However, Vitamin D disorders and hypomagnesemia were not associated with mortality. **Conclusions:** The results of the present study revealed that Vitamin D disturbances, but not hypomagnesemia, are associated with the severity of SARS-CoV-2.

**Keywords:** Coronavirus disease 19. Magnesium. Mortality. Severity. Vitamin D.

### Resumen

**Objetivo:** Determinar la asociación entre los niveles séricos de vitamina D y de magnesio con la gravedad y la mortalidad de la COVID-19 en pacientes hospitalizados. **Método:** Hombres y mujeres mayores de 18 años con probable COVID-19 fueron enrolados en un estudio de casos y controles. Los pacientes con una prueba positiva o negativa para SARS-CoV-2 fueron asignados en los grupos de casos y de controles, respectivamente. **Resultados:** Un total de 54 pacientes, 30 mujeres y 24 hombres, fueron enrolados y asignados a los grupos COVID-19 (n = 27) y control (n = 27). El análisis de regresión logística mostró que la deficiencia de vitamina D (odds ratio [OR]: 6.13; intervalo de confianza del 95% [IC95%]: 1.32-28.34) y la insuficiencia de vitamina D (OR: 0.12; IC95%: 0.02-0.60) se asocian significativamente con hospitalización. Sin embargo, las alteraciones de la vitamina D y la hipomagnesemia no se asociaron con mortalidad. **Conclusiones:** Los resultados del presente estudio revelaron que las alteraciones de la vitamina D, pero no la hipomagnesemia, se asocian con la gravedad de la COVID-19.

**Palabras clave:** COVID-19. Magnesio. Mortalidad. Gravedad. Vitamina D.

#### \*Correspondence:

Luis E. Simental-Mendía

E-mail: luis\_simental81@hotmail.com

2444-0507/© 2023 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Date of reception: 10-12-2023

Date of acceptance: 30-12-2023

DOI: 10.24875/CIRUE.M23000744

Cir Cir (Eng). 2024;92(5):590-594

Contents available at PubMed

[www.cirugiaycirujanos.com](http://www.cirugiaycirujanos.com)

## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a multiorgan disease with inflammatory and prothrombotic characteristics<sup>1,2</sup>. The number of SARS-CoV-2 cases increased rapidly worldwide and, in Mexico, hospitals and emergency services were modified for the specialized treatment of coronavirus disease 19 (COVID-19) patients<sup>3,4</sup>. Through the angiotensin-converting enzyme 2 (ACE-2) receptor, this virus infects lung epithelial cells and macrophages, leading to the activation of macrophages, neutrophils, and T cells, causing sustained elevations of pro-inflammatory cytokines such as interleukin-1, 6 and tumor necrosis factor alpha. In this context, the “cytokine storm,” a hyperinflammatory state triggered by SARS-CoV-2, is responsible for some of the most severe complications of COVID-19, including acute respiratory distress syndrome (ARDS). Although the inflammatory response initially helps to eliminate pathogens, it also damages the alveolar endothelial-epithelial barrier, resulting in edema and thrombosis, which in turn causes apoptosis of Type 2 pneumocytes and, in some patients, ARDS<sup>2</sup>.

Magnesium is an essential mineral for basic biochemical reaction, physiological functions and metabolism in the human body<sup>5-8</sup>. In addition, this element has anti-inflammatory, antioxidant, anti-spasm, vasodilation, and neuroprotection effects<sup>9</sup> and plays an important role in the regulation of the immune response through immunoglobulin synthesis, immune cell adherence, antibody-dependent cytotoxicity, immunoglobulin M lymphocyte binding, macrophage response to lymphokines, and T helper-B cell adherence, especially in viral infections<sup>10</sup>. Therefore, it has been hypothesized that subjects with hypomagnesemia are at higher risk of developing respiratory tract infections<sup>11</sup>.

Magnesium is fundamental in the synthesis, transport, and activation of Vitamin D, since acts as a cofactor for the enzymes involved in its metabolism<sup>12</sup>. Vitamin D confers a protective effect against respiratory tract infections by inhibiting the hyperinflammatory response through the regulation of cytokines and differentiation of T cells<sup>12-14</sup>. Furthermore, some authors have suggested that Vitamin D may downregulate ACE-2 receptors, resulting in a protective effect against fibrosis of COVID-19 by accelerating the healing process in the lung tissue<sup>15</sup>. Thus, the objective of this study was to determine the association between serum Vitamin D and magnesium levels with severity and mortality in hospitalized patients diagnosed with COVID-19.

## Materials and methods

With prior approval by the Ethics and Research Committee of the Hospital Salvador Zubirán Anchondo from Chihuahua, Mexico (registration number 0294), and following the principles of the Helsinki Declaration, a cross-sectional and longitudinal study was conducted. Men and women over 18 years of age with probable pulmonary infection were considered to participate in this study after acceptance of the informed consent. After admission in the emergency service, patients were assessed through standardized interviews, clinical examination, and laboratory tests including reverse transcriptase-polymerase chain reaction test for SARS-CoV-2. According to the result of this last test, participants were assigned into the groups with (positive test) or without (negative test) COVID-19. Exclusion criteria were pregnancy, chronic diarrhea, chronic kidney disease, heart failure, cancer, and the supplement intake during the last 4 weeks before the study. Hospitalized patients were followed until discharge due to recovery or death, including the admission to the intensive care unit (ICU).

## Definitions

Hypomagnesemia was defined by serum levels < 1.8 mg/dL and Vitamin D deficiency by concentrations < 20 ng/mL, and Vitamin D insufficiency for concentrations 20 and < 30 ng/mL. Finally, hospitalization and admission to the ICU were considered for severity.

## Assays

The venous blood samples were obtained following 8-10 h overnight fasting. The serum levels of 25-hydroxyvitamin D were determined by electroluminescence method with a coefficient of variation of 6.7 using a COBAS 6000 analyzer (Roche Diagnostics, Germany). The serum magnesium concentrations were measured with quantitative photometric biochemical analysis with a coefficient of variation of 3.8 using the ADVIA 1800 analyzer (Siemens, Tarrytown, NY, USA).

## Statistical analysis

Numerical variables were reported as mean  $\pm$  standard deviation and categorical variables as proportions. Differences between groups were estimated



using unpaired Student's t-test for numerical variables and the  $\chi^2$  test for categorical variables. Multiple logistic regression analysis (adjusted by obesity, diabetes, and hypertension) was performed to assess the association of hypomagnesemia (ordinal variable) and Vitamin D abnormalities (ordinal variables) with SARS-CoV-2 (overall population), severity, and mortality (patients with positive SARS-CoV-2). A 95% confidence interval (95% CI) and  $p < 0.05$  were used to establish statistical significance. The data were analyzed with the IBM SPSS Static Version 15.0.

## Results

A total of 54 patients, 30 women and 24 men, with a mean age of  $53.4 \pm 21.8$  years were enrolled and allocated into the groups with ( $n = 27$ ) and without ( $n = 27$ ) COVID-19.

In the overall population, 78% had low levels of Vitamin D and 55% hypomagnesemia. The most common comorbidities were: diabetes (35%), hypertension (35%), chronic obstructive pulmonary disease 11.1%, liver disease 5%, and asthma 3.7%. However, the distribution of comorbidities between the study groups was similar.

The clinical and biochemical characteristics of the study population are shown in (Table 1). The cases presented a lower oxygen saturation than the controls. There were other significant differences between the study groups.

In addition, a higher percentage of patients with COVID-19 was admitted to the ICU in comparison with the controls (85.1% vs. 33.3%,  $p < 0.001$ ).

Among COVID-19 patients, the multiple logistic regression analysis showed that Vitamin D deficiency (OR = 6.13; 95% CI: 1.32-28.34) and insufficiency (OR = 0.12; 95% CI: 0.02-0.60) are significantly associated with hospitalization (OR = 0.11; 95% CI: 0.02-0.50). However, hypomagnesemia and Vitamin D abnormalities were not associated with mortality (Table 2).

## Discussion

Our results suggest that Vitamin D disorders, but not hypomagnesemia, are associated with the severity of SARS-CoV-2.

Previous studies have reported that low magnesium levels are associated to severity and mortality<sup>16,17</sup>, which is in disagreement with our findings. This inconsistency could be explained because these studies were retrospective analyses that only included patients

with COVID-19 (comparing severe versus non-severe cases), while we conducted a cross-sectional study comparing patients with and without COVID-19. Furthermore, another possible reason is that the frequency of magnesium deficiency in the target population of our study was very high (46.2%) compared to that reported for the adult Mexican population (31%)<sup>18</sup>.

Interestingly, most of our study population had Vitamin D deficiency (74.5%); this finding coincides with another Colombian study where it was found that the male gender and the Fitzpatrick IV phototype were associated with an increased risk of Vitamin D deficiency<sup>19</sup>. Besides, a previous systematic review and meta-analysis revealed that low serum Vitamin D levels are associated with an increased risk of COVID-19 infection<sup>20</sup>. Nonetheless, we observed that Vitamin D deficiency is not associated with the presence of SARS-CoV-2. There are several mechanisms involved in the infection of respiratory viruses by Vitamin D deficiency. In this regard, it has been reported that Vitamin D deficiency affects the immune response, particularly innate immune function. Furthermore, low levels of Vitamin D decrease the active Vitamin D synthesis, leading to the mitigation of the antimicrobial and antiviral properties of this vitamin. Furthermore, Vitamin D regulates the expression of cathelicidin and defensin, molecules that induce the expression of antiviral cytokines and chemokines, resulting in the recruitment of T cells, natural killer cells, neutrophils, monocytes, and macrophages. In addition, Vitamin D induces autophagy in monocytes and macrophages through cathelicidin, Beclin 1, and mTOR pathway<sup>21-23</sup>. Furthermore, Vitamin D stimulates PI3KC3 through upregulation of intracellular calcium and nitric oxide, which promotes autophagy<sup>24</sup>. Therefore, the protective actions of Vitamin D may be mitigated by its deficiency, causing a defective response against respiratory viruses, including SARS-CoV-2<sup>25</sup>.

It is noteworthy that the results of our study showed that Vitamin D deficiency was not associated with severity and mortality, which is in contrast with several studies. In this regard, it has been reported that advanced age is an important risk factor for the severity and mortality in patients with COVID-19<sup>26</sup>; however, the target population of our study had a mean age  $< 60$  years, which could explain our results. However, in the sub analysis of patients with SARS-CoV-2, Vitamin D deficiency ( $n = 18$ ) and insufficiency ( $n = 4$ ) were associated with hospitalization. Nevertheless, it is important to note that these results were obtained from a smaller sample size, which could explain the direct and inverse association of Vitamin D deficiency

**Table 1. Clinical and biochemical characteristics of the study population, n = 54**

Variables	Overall (n = 54)	SARS-CoV-2 (+) (n = 27)	SARS-CoV-2 (-) (n = 27)	p
Age, years	53.4 ± 22.0	52.5 ± 22.4	54.3 ± 21.9	0.77
Women, n (%)	24 (44.4)	14 (51.8)	16 (59.2)	0.78*
Body mass index, kg/m <sup>2</sup>	25.3 ± 32.2	26.2 ± 5.8	24.5 ± 5.0	0.23
Systolic blood pressure, mmHg	113.5 ± 32.2	110.1 ± 6.5	116.8 ± 30.3	0.45
Diastolic blood pressure, mmHg	74.0 ± 20.8	71.1 ± 21.9	77.0 ± 19.5	0.29
Oxygen saturation, %	84.7 ± 7.4	81.5 ± 8.7	87.9 ± 3.9	0.001
Magnesium, mg/dL	1.9 ± 0.9	1.9 ± 0.6	1.8 ± 0.4	0.50
Vitamin D, ng/mL	15.8 ± 7.0	15.1 ± 5.0	16.5 ± 8.6	0.48
Days of hospitalization	6.3 ± 5.9	12.3 ± 9.5	11.1 ± 8.9	0.92
Deaths, n (%)	21 (38.8)	13 (48.1)	8 (29.6)	0.16*
APACHE II score	11.9 ± 9.3	12.3 ± 9.5	11.1 ± 8.9	0.81
SOFA score	5.8 ± 3.6	4.8 ± 3.5	6.7 ± 3.5	0.06

Values are mean ± standard deviation. P value estimated with the Student's t-test. \*p value estimated with the  $\chi^2$  test. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

**Table 2. Multiple logistic regression analysis that evaluates the association between low levels of magnesium and Vitamin D (independent variables) with SARS-CoV-2 and their outcomes (dependent variables). The normal values of magnesium and Vitamin D were used as reference groups**

Independent variables	SARS-CoV-2 (+)*	Hospitalization**	ICU admission**	Death**
	OR (95% CI) <sup>†</sup>	OR (95% CI) <sup>†</sup>	OR (95% CI) <sup>†</sup>	OR (95% CI) <sup>†</sup>
Hypomagnesemia (< 1.8 mg/dL)	0.54 (0.16-1.77)	0.61 (0.16-2.27)	0.78 (0.25-2.37)	1.08 (0.34-3.39)
Vitamin D deficiency (< 20 ng/mL)	2.36 (0.54-10.30)	6.13 (1.32-28.34)	2.79 (0.70-11.13)	2.87 (0.62-13.20)
Vitamin D insufficiency (20 < 30 ng/mL)	0.51 (0.11-2.24)	0.12 (0.02-0.60)	0.27 (0.06-1.14)	0.20 (0.38-1.15)
Magnesium and Vitamin D deficiencies	0.92 (0.25-3.32)	1.29 (0.27-6.12)	2.04 (0.55-7.54)	2.32 (0.65-8.17)

OR: odds ratio; CI: confidence interval; ICU: intensive care unit. \*Analysis conducted in the overall population. \*\*Analysis conducted in patients with SARS-CoV-2 (+). <sup>†</sup>Analysis adjusted by obesity, diabetes, and hypertension. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

and insufficiency, respectively. Therefore, these findings could be treated with caution.

A previous meta-analysis revealed that Vitamin D supplementation prevents against acute respiratory tract infection<sup>27</sup>. In this context, a randomized controlled trial showed that a high-dose Vitamin D supplementation turned SARS-CoV-2 RNA negative in Vitamin D-deficient individuals with COVID-19 infection<sup>28</sup>. Another randomized clinical trial suggested that a high dose of Vitamin D improves the clinical course of COVID-19 infection through the suppression of cytokine storms<sup>29</sup>. According to the abovementioned, Vitamin D supplementation may be a promising treatment for COVID-19 in vitamin deficient patients. However, larger randomized controlled trials are mandatory

to corroborate the potential beneficial effects of this vitamin on outcomes of COVID-19 infection.

This study has some limitations that should be mentioned. First, taking into account the study design, causality cannot be assured. Second, we recognize the small sample size, which may introduce a potential source of bias. Finally, it is important to note that this study was conducted during the winter, resulting in an increased incidence of respiratory tract infections and reduced sun exposure, which could affect our results.

## Conclusion

The results of the present study showed that Vitamin D abnormalities are associated with the severity of

SARS-CoV-2. However, low magnesium and Vitamin D levels are not related with the mortality by COVID-19.

## Acknowledgments

The authors would like to thank Q.B.P. Miriam Márquez Córdova and Dr. Rubén Cuevas Martínez of the Hospital General Salvador Zubirán in Chihuahua, Chih. and the collaborators who helped with the measurements of Vitamin D and magnesium levels.

## Funding

The authors declare that they have not received funding.

## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

## References

1. Tan CW, Ho LP, Kalimuddin S, Cherng BP, Teh YE, Thien SY, et al. Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B12 in combination on progression to severe outcomes in older patients with coronavirus (COVID-19). *Nutrition*. 2020;79-80:111017.
2. Cooper ID, Crofts CA, DiNicolantonio JJ, Malhotra A, Elliott B, Kyriakidou Y, et al. Relationships between hyperinsulinaemia, magnesium, vitamin D, thrombosis and COVID-19: rationale for clinical management. *Open Heart*. 2020;7:e001356.
3. Serrano-González SP, Nájera-Reyes JA, Ortiz-Mendoza CM. Changing characteristics of emergency surgery during COVID-19 pandemic: a retrospective cohort study. *Cir Cir*. 2022;90:13-7.

4. Bozada-Gutiérrez K, Trejo-Ávila M, Moreno-Portillo M. Postoperative complications and predictors of mortality in patients with COVID-19. *Cir Cir*. 2023;91:344-53.
5. Komiya Y, Runnels LW. TRPM channels and magnesium in early embryonic development. *Int J Dev Biol*. 2015;59:281-8.
6. Ohyama T. New aspects of magnesium function: a key regulator in nucleosome self-assembly, chromatin folding and phase separation. *Int J Mol Sci*. 2019;20:4232.
7. Flatman PW. Magnesium transport across cell membranes. *J Membr Biol*. 1984;80:1-14.
8. Quilliot D, Bonsack O, Jaussaud R, Mazur A. Dysmagnesemia in Covid-19 cohort patients: prevalence and associated factors. *Magnes Res*. 2020;33:114-22.
9. Tang CF, Ding H, Jiao RQ, Wu XX, Kong LD. Possibility of magnesium supplementation for supportive treatment in patients with COVID-19. *Eur J Pharmacol*. 2020;886:173546.
10. Liang RY, Wu W, Huang J, Jiang SP, Lin Y. Magnesium affects the cytokine secretion of CD4<sup>+</sup> T lymphocytes in acute asthma. *J Asthma*. 2012;49:1012-5.
11. Iotti S, Wolf F, Mazur A, Maier JA. The COVID-19 pandemic: is there a role for magnesium? Hypotheses and perspectives. *Magnes Res*. 2020;33:21-7.
12. Dai Q, Zhu X, Manson JA, Song Y, Li X, Franke AA, et al. Magnesium status and supplementation influence vitamin D status and metabolism: results from a randomized trial. *Am J Clin Nutr*. 2018;108:1249-58.
13. Mohan M, Cherian JJ, Sharma A. Exploring links between vitamin D deficiency and COVID-19. *PLoS Pathog*. 2020;16:e1008874.
14. Autier P, Mullie P, Macacu A, Dragomir M, Boniol M, Coppens K, et al. Effect of vitamin D supplementation on non-skeletal disorders: a systematic review of meta-analyses and randomised trials. *Lancet Diabetes Endocrinol*. 2017;5:986-1004.
15. Arboleda JF, Urcuqui-Inchima S. Vitamin D supplementation: a potential approach for coronavirus/COVID-19 therapeutics? *Front Immunol*. 2020;11:1523.
16. Alamdari NM, Afaghi S, Rahimi FS, Tarki FE, Tavana S, Zali A, et al. Mortality risk factors among hospitalized COVID-19 patients in a major referral center in Iran. *Tohoku J Exp Med*. 2020;252:73-84.
17. Zeng HL, Yang Q, Yuan P, Wang X, Cheng L. Associations of essential and toxic metals/metalloids in whole blood with both disease severity and mortality in patients with COVID-19. *FASEB J*. 2021;35:e21392.
18. Mejía-Rodríguez F, Shamah-Levy T, Villalpando S, García-Guerra A, Humarán IM. Iron, zinc, copper and magnesium deficiencies in Mexican adults from the National Health and Nutrition Survey 2006. *Salud Publica Mex*. 2013;55:275-84.
19. Daza AM, Casanova ME, Rojas NA, Triana OJ, Ocampo MB. Prevalence and factors associated with vitamin D deficiency in young adults of two higher education institutions in Cali and Bogotá: a cross-sectional study. *Rev Colomb Endocrinol Diabetes Metab*. 2020;7:12-8.
20. Teshome A, Adane A, Girma B, Mekonnen ZA. The impact of vitamin D level on COVID-19 infection: systematic review and meta-analysis. *Front Public Health*. 2021;9:624559.
21. Wang J. Beclin 1 bridges autophagy, apoptosis and differentiation. *Autophagy*. 2008;4:947-8.
22. Jang W, Kim HJ, Li H, Jo KD, Lee MK, Song SH, et al. 1,25-dihydroxyvitamin D attenuates rotenone-induced neurotoxicity in SH-SY5Y cells through induction of autophagy. *Biochem Biophys Res Commun*. 2014;451:142-7.
23. Yuk JM, Shin DM, Lee HM, Yang CS, Jin HS, Kim KK, et al. Vitamin D3 induces autophagy in human monocytes/macrophages via cathelicidin. *Cell Host Microbe*. 2009;6:231-43.
24. Uberti F, Lattuada D, Morsanuto V, Nava U, Bolis G, Vacca G, et al. Vitamin D protects human endothelial cells from oxidative stress through the autophagic and survival pathways. *J Clin Endocrinol Metab*. 2014;99:1367-74.
25. Bilezikian JP, Bikle D, Hewison M, Lazaretti-Castro M, Formenti AM, Gupta A, et al. Mechanisms in endocrinology: vitamin D and COVID-19. *Eur J Endocrinol*. 2020;183:R133-47.
26. Hua W, Xiaofeng L, Zhenqiang B, Jun R, Ban W, Liming L. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2020;41:297-300.
27. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ*. 2017;356:i6583.
28. Rastogi A, Bhansali A, Khare N, Suri V, Yaddanapudi N, Sachdeva N, et al. Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study). *Postgrad Med J*. 2022;98:87-90.
29. Sarhan N, Abou Warda AE, Sarhan RM, Boshra MS, Mostafa-Hedeab G, ALruwaili BF, et al. Evidence for the efficacy of a high dose of vitamin D on the hyperinflammation state in moderate-to-severe COVID-19 patients: a randomized clinical trial. *Medicina (Kaunas)*. 2022;58:1358.

# Modified extensile calcaneal exposure is safe

## *La exposición extensible modificada del calcáneo es segura*

Chuansheng Fu<sup>1</sup>, Baofu Wei<sup>1</sup>, Hongjian Pei<sup>1</sup>, Cunyin Xue<sup>1</sup>, Jijuan Zhou<sup>2</sup>, and Guodong Zhong<sup>2\*</sup>

<sup>1</sup>Department of Hand and Foot Surgery, Linyi People's Hospital, Linyi; <sup>2</sup>Academician Gu Yudong Workstation of Heze Bo'ai Hospital, Heze, China

### Abstract

**Objective:** The objective of this study was to evaluate the effect of open reduction and internal fixation for displaced intra-articular calcaneal fractures through a modified tarsal sinus incision. **Methods:** A retrospective review over 3 years of the clinical data of patients with intra-articular calcaneal fractures treated with open reduction and internal fixation through lateral hook curvy incisions. The efficacy of the 25 lateral hook curvy incisions was analyzed. **Results:** According to the AOFAS hindfoot function scoring criteria, there were 20 excellent (80%), 2 good (8%), 2 fair (8%), and 1 poor patient outcome. The average pre-operative Bohler's angle was  $6.8 \pm 8.9^\circ$ , and the average angle at follow-up was  $33.6 \pm 5.7^\circ$ . The average pre-operative Gissane angle was  $89.2 \pm 20.0^\circ$ , and the average angle at follow-up was  $115.5 \pm 5.5^\circ$ . **Conclusions:** A lateral hook curvy incision can expose the posterior articular surface of the calcaneus and the calcaneocuboid joint, reduce stripping and pulling of the soft tissue, and avoid calcaneus valgus caused by the pulling of the peroneus tendon.

**Keywords:** Calcaneal fracture. Hook curvy incision. AOFAS hindfoot function score. Bohler's angle.

### Resumen

**Objetivo:** Evaluar el efecto de la reducción abierta y la fijación interna de las fracturas de calcáneo intraarticulares desplazadas a través de una incisión del seno tarsiano modificada. **Métodos:** Revisión retrospectiva de 3 años de los datos clínicos de pacientes con fracturas intraarticulares de calcáneo tratadas con reducción abierta y fijación interna a través de incisiones laterales curvadas en gancho. Se analizó la eficacia de la incisión curvada con 25 ganchos laterales. **Resultados:** Según los criterios de puntuación de la función del retropié de la AOFAS, hubo 20 resultados excelentes (80%), 2 buenos (8%), 2 regulares (8%) y 1 pobre. El ángulo de Bohler preoperatorio promedio fue de  $6.8 \pm 8.9^\circ$  y el ángulo promedio en el seguimiento fue de  $33.6 \pm 5.7^\circ$ . El ángulo de Gissane preoperatorio promedio fue de  $89.2 \pm 20.0^\circ$  y el ángulo promedio en el seguimiento fue de  $115.5 \pm 5.5^\circ$ . **Conclusiones:** Una incisión curvada en gancho lateral puede exponer la superficie articular posterior del calcáneo y la articulación calcaneocuboidea, reducir el desprendimiento y la tracción del tejido blando, y evitar el calcáneo valgo causado por tracción del tendón peroneo.

**Palabras clave:** Fractura de calcáneo. Incisión curvada en gancho. Puntuación AOFAS de función del retropié. Ángulo de Bohler.

### \*Correspondence:

Guodong Zhong

E-mail: zhongguod08@163.com

2444-0507/© 2024 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Date of reception: 13-11-2023

Date of acceptance: 06-03-2024

DOI: 10.24875/CIRUE.M24000745

Cir Cir (Eng). 2024;92(5):595-604

Contents available at PubMed

[www.cirugiaycirujanos.com](http://www.cirugiaycirujanos.com)



## Introduction

Due to the special anatomical position and irregular stereotypical structure of the calcaneus bone, calcaneal fracture surgeries present difficulties related to exposure, reduction, and fixation and are accompanied by many post-operative complications<sup>1</sup>. The most common complication associated with the surgical treatment of calcaneus fractures is delayed wound healing, likely a reflection of the limited surrounding soft-tissue envelope, as well as the extent of soft-tissue trauma associated with the injury. The most common neurological complication following operative treatment of fractures of the calcaneus is an iatrogenic injury to a sensory cutaneous nerve, particularly the sural nerve, during an extensile lateral approach<sup>2</sup>. Effective treatment of displaced intra-articular calcaneal fractures is challenging for all orthopedic surgeons. Proper incisions can fully reveal the fractured end of the calcaneal bone and the collapsed joint surface, which is conducive to reduction and fixation and reducing incision-related complications. This is a key to the treatment of displaced intra-articular calcaneal fractures. The extensile lateral L-shaped approach to the calcaneus is the method for surgical fixation of displaced intra-articular calcaneus fractures<sup>3,4</sup>. Related complications such as incision infection, non-healing incisions, skin necrosis, and nerve injuries are frequently reported<sup>4,5</sup>, and the occurrence of any problem will affect the patient's recovery. Although the sinus tarsi approach and the enlarged sinus tarsi approach can reduce incision-related complications, their application has limitations; mainly for Sanders II and III AB type fractures<sup>6-8</sup>. The coronal view of the calcaneus model was used to demarcate the maximum length of the connection between the talus and calcaneus. This gap between talus and calcaneus is divided into three equal parts through three points: a, b, and c; the lateral point of sustentaculum tali is marked as point c. Based on points a, b, and c, three fracture lines were depicted as A, B, and C according to the Sanders system of classification. The model with double fracture lines (AB, AC, or BC) represented the Sanders Type III (AB, AC, BC) fracture<sup>9</sup>.

With the continuous development and progress of minimally invasive technology, modified incision of the tarsal sinus can greatly reduce the incision range but has no impact on the full exposure of the subtalar articular surface. Doctors can also perform fracture reduction under direct vision, and this approach can

reduce the damage to the blood supply to the foot and ankle. The purpose of the current study was to describe a modified tarsal sinus incision and evaluate the results of open reduction and internal fixation through the modified tarsal sinus incision as a surgical treatment of displaced intra-articular calcaneal fractures.

## Methods

### *Patients and methods*

The clinical data of patients with intra-articular calcaneus fractures treated by open reduction and internal fixation through a lateral hook curvy incision from May 2014 to July 2017 were analyzed retrospectively. The inclusion criteria were acute calcaneal fractures (within 2-3 weeks) involving the joints and Type II and III fractures, based on the Sanders classification<sup>10</sup>. The exclusion criteria were patients with old calcaneal fractures, Type I and IV fractures based on the Sanders classification, extra-articular fractures, and calcaneus fracture of a diabetic foot.

A total of 139 patients with calcaneal fractures admitted to our hospital were retrospectively analyzed. Among them, 13 cases of old calcaneal fractures, 28 cases of Sanders Type I and Type IV fractures, 16 cases of extra-articular fractures, and three cases of diabetic foot were excluded from the study. In 79 patients with calcaneal intra-articular fractures, 25 patients were treated with open reduction and internal fixation using a lateral hook incision.

Among the 25 patients included in this study, 21 were men and four were women. The average age was 44.6 years (range: 25-64 years). The right side was involved in 11 cases, the left side in 10 cases, and bilateral calcaneus fractures were present in four cases. The mechanism of injury was a fall from height in 22 patients and a traffic accident in one case, a heavy pound injury in one case, and falling in one case.

Twenty-five feet had closed fractures, and four cases were open fractures. Two patients had associated lumbar compression fractures and pelvic fractures without surgical treatment. One case had an associated radial fracture with open reduction and internal fixation. One case had an associated lateral malleolar fracture. One patient had an open fracture with a medial soft-tissue defect, and a secondary flap graft was performed to repair the wound.

At the time of admission to the hospital, anteroposterior, lateral, and internal oblique radiographs of the injured foot and an axial radiograph of the fractured calcaneus were taken. A pre-operative CT scan was made for all cases to evaluate the size of the displaced fracture fragments and help the surgeons reduce the displaced fracture fragments. From the plain radiographs, the pre-operative Bohler angle and Gissane angle were measured. The posterior articular surface was divided into three columns by two fracture lines according to the coronal view of CT images. Line C separated the medial fragment from the posterior talar facet of the calcaneus<sup>11,12</sup>. There were 15 cases of Type II fractures, seven Type IIA, and eight Type IIB. Fourteen cases were Type III fractures, 10 were Type IIIAB, one was Type IIIAC, and three were Type IIIIC. In 18 patients with calcaneal fractures, the calcaneocuboid joint surface was involved. If the wrinkle sign was observed at the lateral side of the heel, surgery was performed.

Patients were clinically evaluated using the AOFAS ankle–hindfoot score (best score = 100 points)<sup>6</sup>. This clinical rating system combines subjective scores of pain and function provided by the patient with objective scores based on the surgeon's physical examination of the patient (to assess sagittal motion, hindfoot motion, ankle–hindfoot stability, and alignment of the ankle–hindfoot). The scale includes nine items that can be divided into three subscales (pain, function, and alignment). Pain comprises one item with a maximum score of 40 points, indicating no pain. Function comprises seven items with a maximum score of 50 points, indicating full function. Alignment comprises one item with a maximum score of 10 points, indicating good alignment. The maximum score is 100 points, indicating no symptoms or impairments. The AOFAS score was divided into groups according to the literature: a score of 90–100 was graded as an excellent result, 75–89 as good, 50–74 as fair, and < 49 points was graded as a failure or poor outcome<sup>3</sup>.

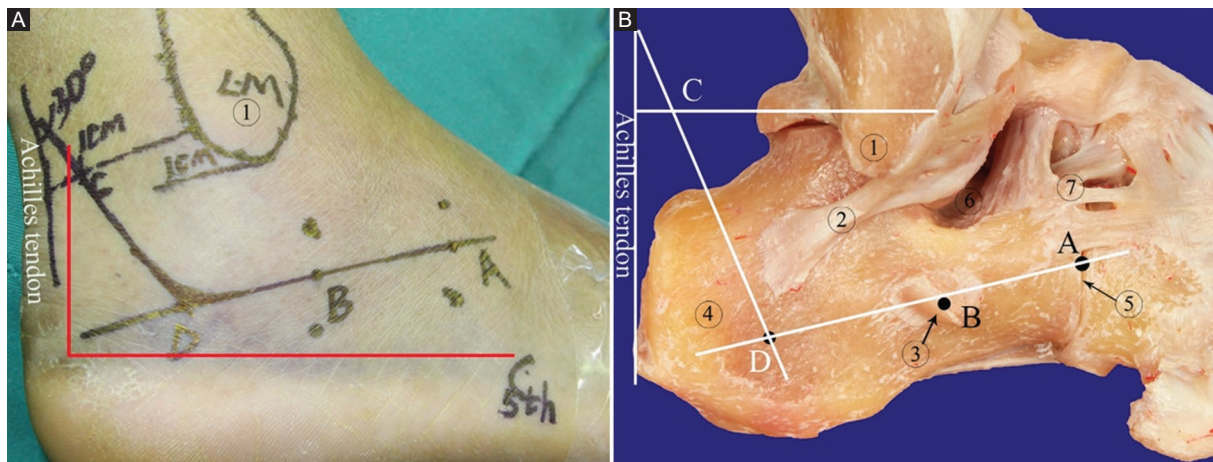
### ***Anatomical basis and design of the modified tarsal sinus incision***

**Incision design:** an incision was made in the side midline of the calcaneus to open the flap on both sides to render calcaneus exposure and operation easier. Accordingly, the central point of the calcaneocuboid joint was A, and the middle point from the bottom of the sinus tarsus to the metatarsal side of the

calcaneus was B. A line was made through A and B. Point C was the intersection point of a 1 cm horizontal line in front of the Achilles tendon and a vertical line to the Achilles tendon from 1 cm above the lateral malleolus. Point D was the intersection of the extension line at a 30° angle between point C and the Achilles tendon and the extension line at two points, A and B. Points C, D, and A were connected into a hook curvy incision, which was extended to both ends through points A and C as required (Fig. 1A). The incision line corresponded to the midline of the lateral wall of the calcaneus, which is the approach for exposing the subtalar joint and the calcaneocuboid joint (Fig. 1B).

**Anatomical basis:** the blood supply of the lateral calcaneus region derives from the arterial network comprising the lateral calcaneus artery, sinus tarsus artery, lateral tarsal artery, and basolateral plantar artery, and rich vascular chains form in the skin and subcutaneous tissue (Fig. 2A)<sup>13,14</sup>. Although the plantar and lateral skin of the heel is supplied by different angiosomes, this is also the anatomical basis of the laterally expanded L-shaped incision. However, there is an extensive vascular network between the two angiosomes at the lateral side and the plantar skin junction of the heel. Anatomical specimens perfused solely through the anterior tibial artery showed an extensive vascular network between the lateral region and pelma of the heel. The skin below the midline of the calcaneus can also obtain blood supply through the traffic branch of the lateral tarsal artery (Fig. 2B).

The sural nerve is accompanied by a small saphenous vein, wound to the lateral heel below the lateral malleolus, runs parallel to the pelma of the foot, and at the front of the calcaneus, moves obliquely across the peroneus brevis tendon and the peroneus longus tendon to the dorsolateral foot to become the lateral dorsal cutaneous nerve of the foot (Fig. 2C). The sural nerve is a cutaneous nerve. When injured, it mainly causes numbness and paresthesia in the innervated area of the nerve, which can be manifested as numbness in the posterolateral area of the calf, the lateral ankle area, the dorsolateral area of the foot, and the skin of the fourth and fifth toes. The fibular nerve is divided into two-to-three lateral cutaneous nerves behind the lateral malleolus, run downward perpendicular to the foot, and are distributed in the lateral skin of the heel. The proximal part of the sural nerve and the small saphenous vein are included in the flap located proximal to the incision, and the distal part is located in the flap of the distal end of the incision. The



**Figure 1.** The design of the modified tarsal sinus incision. **A:** the line ABDC is the lateral hook curvy incision. **B:** the relationship between the lateral hook curvy incision and calcaneus. a: The midpoint of the calcaneocuboid joint. b: The calcaneal midpoint at the level of the sinus. c: The intersection point of 1 cm horizontal line in front of the Achilles tendon and vertical line to the Achilles tendon from 1 cm above the lateral malleolus. d: The intersection point of slash at a 30 less tendon and vertical line to the Achilles tendon f connection.

1: The lateral malleolus; 2: calcaneofibular ligament; 3: peroneal trochlea; 4: calcaneal tuberosity; 5: Calcaneocuboid joint; 6: Tarsal sinus; 7: Anterior tubercle of calcaneus. The red line is the extended lateral L-shaped approach.

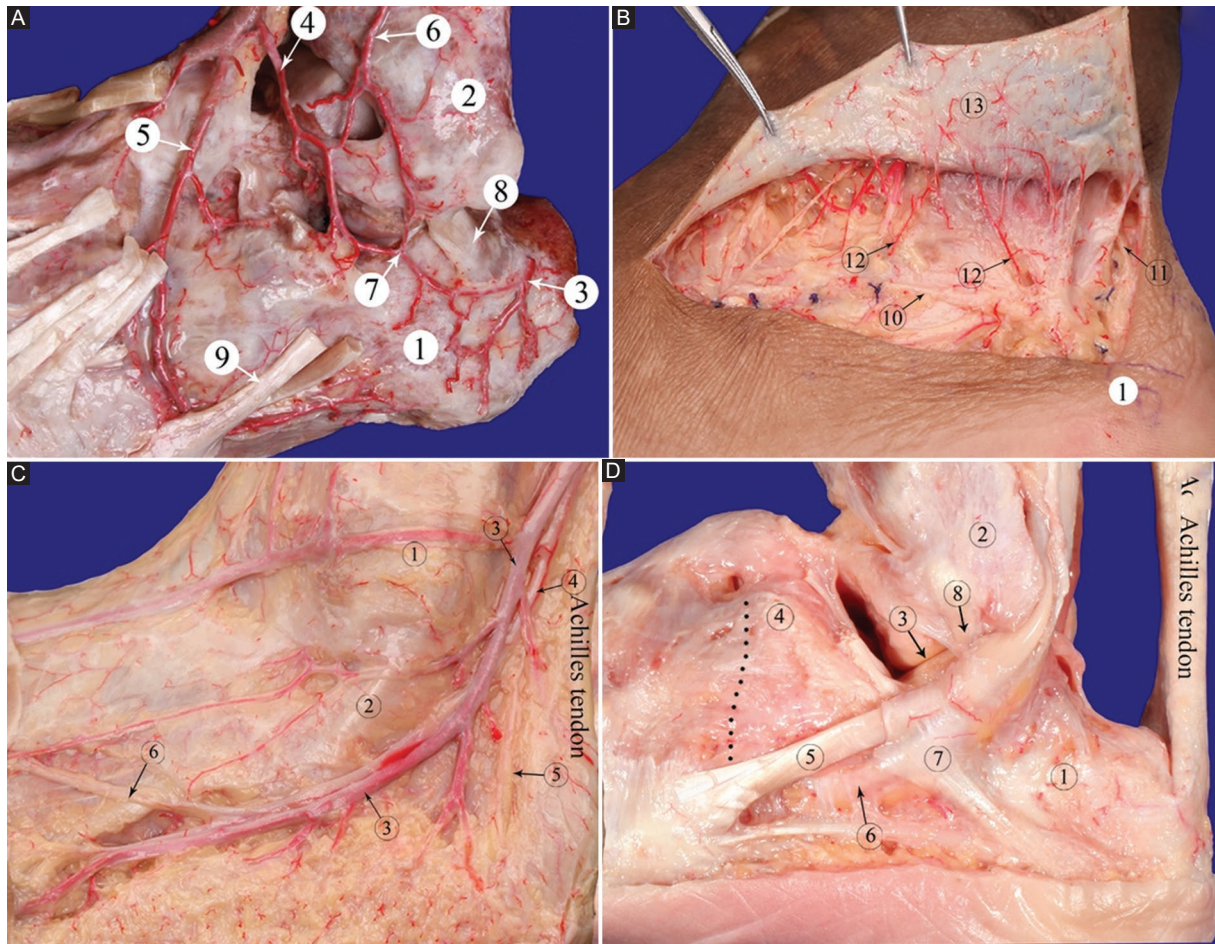
peroneus brevis tendon runs obliquely forward and down the lateral side of the calcaneus, from the back upward and is attached to the lateral calcaneal wall by the inferior peroneal retinaculum (Fig. 2D). The anterior tubercle of the calcaneus and calcaneocuboid joint is located above the front of the peroneal tendon. The peroneal tendon should be pulled down to expose the calcaneocuboid joint and the base of the sinus tarsus. The subtalar articular surface can be clearly exposed through the tarsal sinus, and a Kirschner wire (K-wire) can be inserted to poke the collapsed articular surface through this gap.

### Surgical technique

The patients were positioned on the uninjured side with the ankle joint in a neutral position. Surgical pads were folded into squares and placed under the medial malleolus. The heel was slightly inverted in the air. The procedure was performed under a femoral tourniquet. (1) The skin and subcutaneous tissue were cut according to the hook curvy incision line, and the bleeding was carefully stopped (ligation and hemostasis; electric knife used with caution). The peroneal nerve was exposed on the superficial layer of the peroneal tendon, distal to the incision, and was freed and protected (Fig. 3A). (2) At the proximal side of the incision, a cut was made vertically to the periosteum without separation from deep tissue. The lateral calcaneal cutaneous nerve was severed. The lateral

calcaneal artery was ligated for hemostasis. A separation was made along the periosteal surface to the malleolar tip, and the calcaneofibular ligament was cut to expose the subtalar articular surface. A separation was made along the surface of the periosteum in the middle of the incision through the deep layer of the peroneus brevis tendon and peroneus longus tendon. An attempt was made to free and protect the peroneus tendon sheath as much as possible to expose the tarsal sinus. A separation was made above the peroneus brevis tendon distal to the incision. The stop point of the extensor digitorum brevis was separated to expose the sinus tarsus, the anterior tubercle of the calcaneus, the calcaneocuboid joint, and the dorsal calcaneocuboid ligament. The proximal peroneus longus tendon was punctured with one-to-two 1.5 K-wires to the external malleolus, the flap was straightened, and the needle was slightly bent to the proximal end. Attention was paid not to squeeze the flap. A 1.5 K-wire was inserted into the talus neck through the front of the peroneus brevis tendon. The flap was straightened and bent medially. As this was necessary, the deep flap was slightly stripped on the surface of the peroneal tendon to reduce flap tension. (3) A large surgical towel was placed under the inner malleolus, and the calcaneus bone was slightly inverted. Slight poking at the subtalar joint with a 3.5 K-wire revealed the posterior articular surface of the calcaneus, and the collapsed posterior articular surface was restored through the sinus tarsal poking using the K-wire for





**Figure 2.** A: the artery network of the lateral area of the calcaneus. B: the extensive subcutaneous capillary network in the proximal end of the hook-curved incision. C: the sural nerve and less saphenous vein. D: the lateral wall of the calcaneus and the peroneal tendons.

1: Calcaneus; 2: lateral malleolus; 3: the lateral calcaneal artery; 4: tarsal sinus artery; 5: lateral tarsal artery; 6: descending branch of external superior malleolus artery; 7: communicating branches; 8: calcaneofibular ligament; 9: tendon of peroneus brevis; 10: the sural nerve; 11: subdermal vascular plexus; 12: Perforating Vessels. c1: the lateral malleolus; c2: tendon of peroneus brevis; c3: the less saphenous vein; c4: the sural nerve; c5: the lateral calcaneal nerve; c6: lateral dorsal cutaneous nerve of foot. d1: calcaneus; d2: lateral malleolus; d3: the subtalar joint; d4: anterior superior tubercle of calcaneus; d5: tendon of peroneus brevis; d6: Peroneus Longus Tendon; d7: retinaculum musculorum peroneorum inferius; d8: calcaneofibular ligament. The black dotted line is the calcaneocuboid joint.

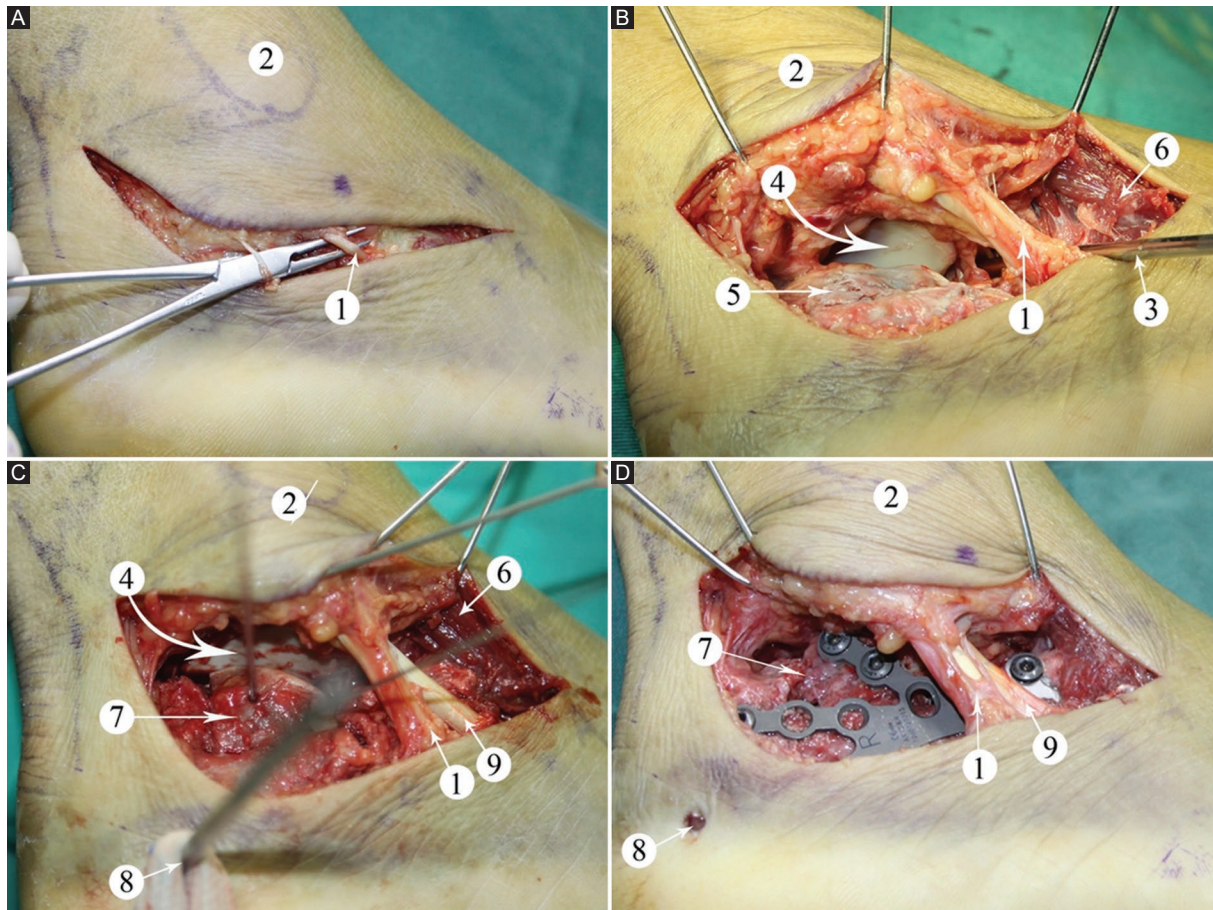
temporary fixation (Figs. 3B and 4). A 3.5 K-wire was placed vertically into the calcaneal tuberosity, which was pulled down slightly to reset. The operator squeezed the calcaneal tuberosity with both hands and turned a K-wire to correct the calcaneus varus. After restoring the joint line of the calcaneal tuberosity, temporary fixation was applied from the calcaneal tuberosity through the posterior articular surface using a K-wire (Fig. 3C). After reduction, one-to-two 2.0 K-wires were temporarily fixed through the calcaneal tubercle to the anterior tubercle of the calcaneus. The calcaneal side and axial radiograph were taken using a C-arm perspective and replaced with the corresponding steel plate/screw fixation (Fig. 3D). (4) The mild valgus position of the heel was maintained, and

a negative pressure drainage tube connected with negative pressure drainage was put in place. Subcutaneous intermittent suturing was performed to reduce the incision tension. Loose vertical mattress-type sutures were used for the incision. Soft gauze compressed the lateral wall of the calcaneus.

### **Post-operative management**

We evaluated the peroneal function within 24 h after the patient's surgery, and the injury mainly caused innervation numbness and paresthesia. On the day after surgery, patients can be instructed to perform back extension, plantar flexion, and straight leg elevation exercises under non-weight-bearing ankle





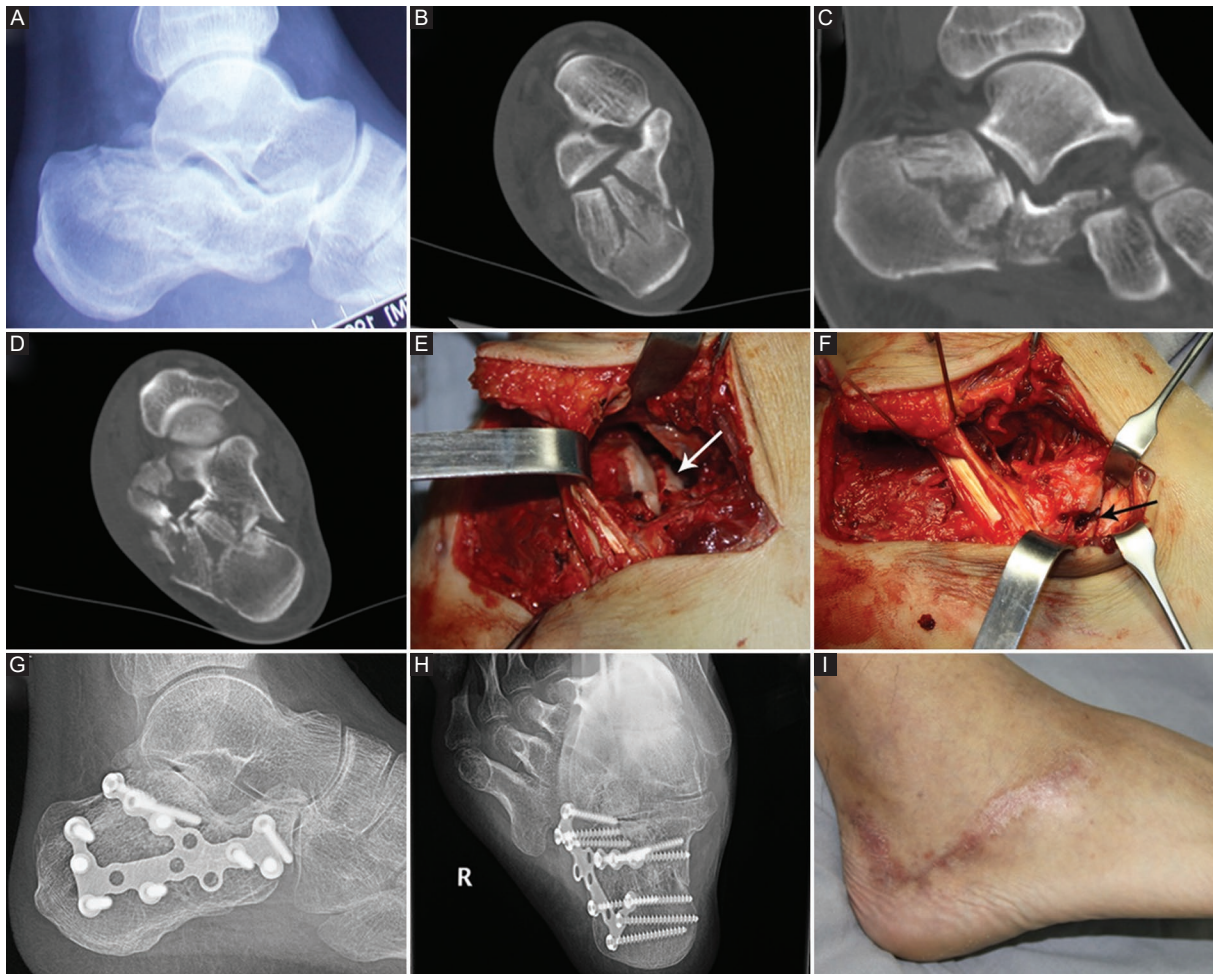
**Figure 3.** A: the incision and sural nerve. B: contactless traction of the Kirschner wire revealed the subtalar joint and the lateral wall of the calcaneus, and the Kirschner wire poke the collapsed articular surface. C: reduce the articular surface, and temporarily fix with the Kirschner wire. D: replace with plate fixation and remove temporary Kirschner wire.  
1: sural nerve; 2: lateral malleolus; 3: Kirschner wire poking articular surface; 4: subtalar articular surface; 5: lateral wall of calcaneus; 6: extensor digitorum brevis; 7: reduction of the collapsed fracture block; 8: Kirschner wire for traction of calcaneal tubercle; 9: tendon of peroneus brevis.

joint conditions. Low-molecular-weight heparin calcium anticoagulant therapy was provided after surgery until discharge. Patients were encouraged to carry partial weight on crutches at 4 weeks after surgery and were allowed to carry full weight when signs of bone healing were observed on re-examination X-rays at 6-10 weeks after surgery. The Bohler and Gissane angles were measured by X-ray 6 months after surgery. All patients were followed up for 2 years to assess their recovery.

## Results

The modified tarsal sinus incision adequately exposed the posterior facet, the lateral wall of the calcaneus, and the calcaneocuboid joint. A traction valgus of calcaneal tuberosity can correct varus deformity. With the talus articular surface as a reference, the inferior talus' articular surface fracture block was restored

through tarsal sinus poking and temporarily fixed with a K-wire (Fig. 4). The articular plane was reduced to squeeze the lateral wall of the calcaneus. Titanium bone plates of appropriate type were selected, trimmed, and shaped according to fracture morphology and then inserted into the lateral calcaneal bone after subperiosteal dissection. After the percutaneous insertion of the guide by the template positioning method, drilling holes and screws were inserted to fix the plate. All 25 cases were followed up for an average of 18.7 (12-24) months. Bone healing was achieved in all patients at 12-month follow-up. The skin incision healed well in all cases without necrosis, infection, or sural nerve damage (Fig. 4). The fracture had healed in all cases after an average period of 8 weeks (6-10 weeks). Due to the different elastic modulus and compositional structure of metal and bone, the stress shielding effect would occur, which could lead to the easy recurrence of fractures



**Figure 4.** A: the lateral view of pre-operative radiographs. B-D: the images of the CT scan, Sanders type III/BC. E: the fracture line of the posterior facet of calcaneus (white arrow). F: the fracture line involved the calcaneocuboid joint (black arrow). G and H: the lateral view and axial view of the post-operative radiographs. I: the healed lateral hook curvy incision.

around the fixed object. Accordingly, the plate-screw internal fixers were removed in 12 patients through the original incision 1-3 years after surgery, and all of the incisions had healed well.

According to the AOFAS ankle-hindfoot score, there were 20 excellent (80%), 2 good (8%), 2 fair (8%), and 1 poor patient (4%) outcomes. The 22 excellent and good cases were rated as satisfactory (88%); the three poor and fair cases were rated as unsatisfactory (12%). Pain at the lateral aspect of the heel was the main complaint of the majority of patients, particularly after long walks and heavy work. Six patients complained of feeling sore and uncomfortable in rainy weather; 12 patients (48%) returned to daily activities but could not bear heavy work; 3 cases (12%) felt mild pain when the surgical area was cold. A slight change in posture was observed in one patient (4%) with a bilateral calcaneal fracture. No pain developed related to irritation by the

internal plate and screws. No cases of subluxation of peroneal tendons could be detected on follow-up. The one poor case (4%) was a patient with bilateral calcaneal fractures, Sanders IV right and Sanders IIAB left type, with poor post-operative recovery. When walking 100 m, the patient experienced unbearable pain, and foot movement was limited. This patient was found to have hyperplasia of the adjacent joints on X-ray 6 months after surgery. The average pre-operative Bohler's angle was  $6.8 \pm 8.9^\circ$ , and the average angle at follow-up was  $33.6 \pm 5.7^\circ$ . The average pre-operative Gissane angle was  $89.2 \pm 20.0^\circ$ , and the average angle at follow-up was  $115.5 \pm 5.5^\circ$ .

## Discussion

Calcaneal fractures are the most common tarsal fractures. Due to their irregular morphological



structure and complex biomechanical functions, calcaneal fractures are considered one of the most challenging fractures, particularly displaced intra-articular calcaneal fractures. Restoring the shape of the articular surface, axis, and length and width of the calcaneus is essential for the recovery of the weight-bearing and walking abilities of the foot. In a randomized controlled trial, Buckley et al. found that patients with displaced intra-articular calcaneal fractures who did not receive worker compensation and underwent surgery had significantly higher satisfaction scores compared to non-surgical patients. The key to surgical treatment of displaced intra-articular calcaneal fractures is to fully expose intra-articular fractures to facilitate anatomical reduction and internal fixation. Open reduction and internal fixation through an extended lateral L-shaped approach have been considered the standard treatment<sup>15</sup>. However, the L-shaped incision was made from 3.5 cm below the lateral ankle along the plantar skin junction to the base of the 5<sup>th</sup> metatarsal bone with this surgical approach, giving rise to disadvantages such as a large dissection range, difficulty exposing the subtalar and calcaneocuboid joint surface, and a high learning curve.

Because the peroneal tendon travels obliquely through the lateral wall of the distal calcaneus, the pulling tendon to the dorsal side indirectly leads to the calcaneus valgus, which is not conducive to the exposure and reduction of the subtalar articular surface. The incidence of complications, such as post-operative incision infection, osteomyelitis, skin margin necrosis, plate exposure, and sural nerve injury is thus high, and the occurrence of complications is inversely correlated with the experience of the surgeon<sup>16</sup>.

With the continued development of minimally invasive and rapid rehabilitation concepts, the treatment of calcaneal fractures using a tarsal sinus incision has gradually been recognized in recent years. Some studies found that the incidence of soft-tissue necrosis, infection, and other complications after tarsal sinus incisions had been reduced to some extent<sup>5,13</sup>. However, this method is only suitable for less displaced intra-articular calcaneal fractures, such as Sanders II and IIIAB fracture types<sup>17</sup>. In addition, this incision has limited exposure to the posterior articular surface and a high learning curve, which limits its clinical application<sup>15</sup>.

The transverse arm of the lateral enlarged L-shaped incision is located between the blood supply area of the lateral and the plantar angiosomes, enabling the raised skin margin to obtain a sufficient blood supply

from the feeding angiosome. Anatomical studies showed the presence of a rich blood supply in the lateral calcaneal region, and its feeding arteries include the lateral calcaneal artery, sinus tarsus artery, and lateral tarsal artery. These arteries have traffic branches that connect to vascular networks. The skin and subcutaneous soft tissue have an extensive vascular network. The lateral region of the heel is also connected to branches of the lateral plantar artery through traffic branches and the vascular network, enabling it to obtain a sufficient blood supply from the pelma area near the plantar region. This is the anatomical basis for the design of the lateral hook curvy incision of the calcaneus. The distal part of the incision can obtain sufficient blood supply from the terminal branches of the plantar and tarsal lateral artery to ensure the survival of the skin margin and significantly reduce the occurrence of complications related to the incision.

Compared with the lateral enlarged L-shaped incision from the metatarsal side of the calcaneus to the proximal end, the lateral hook curvy incision from the midline to the lateral side of the calcaneus is more likely to expose the subtalar joint surface, and the scope of the dissection is small. The hook curvy incision is oblique across the peroneal tendon, and the sinus tarsus and calcaneocuboid joint are exposed above the peroneal tendon, which is more conducive to the reduction and fixation of the fracture when the calcaneocuboid joint is involved. After clearing the tarsal sinus, the collapsed subtalar articular surface can be exposed. With the anterior calcaneus nodule as the fulcrum, a K-wire can be used to poke the collapsed joint surface. At the same time, through the lateral wall extrusion, it is easy to achieve an anatomical reduction of the inferior joint surface and restore the height of the calcaneal bone and the Bohler and the Gissane angles while reducing the dissection of the calcaneal fracture block. The proximal end of the incision may expose the upper edge of the calcaneal tuberosity, facilitating the reduction of the displaced calcaneal tuberosity.

Because the posterior articular surface of the calcaneus is difficult to reveal, and the soft-tissue blood supply of the lateral calcaneus is weak, the selection of appropriate surgical methods is very important for the treatment of calcaneus fractures. The lateral calcaneal L-shape incision is commonly used for the surgical treatment of calcaneal fractures involving the posterior articular surface, as it provides a wide surgical field of view and is firmly fixed with a plate that applies an overall compression force to the calcaneal

bone, thereby restoring calcaneal width and preventing varus and valgus deformities. However, it was reported in the literature that lateral calcaneal L-shaped incision is prone to damaging the lateral calcaneal artery, and the incidence of post-operative soft-tissue necrosis, incision split, exposed plate, and infection is high<sup>18</sup>. In addition, both proximal and distal L-shaped incisions pose a risk of damage to the sural nerve. Therefore, many studies have focused on minimally invasive surgery for calcaneal fractures to minimize soft-tissue damage. The standard tarsal sinus incision is a longitudinal straight incision from the tip of the lateral ankle and extends to the base of the fourth metatarsal bone. As one of the minimally invasive techniques widely used in clinical practice, this approach can directly observe the posterior articular surface, making post-operative incision-related complications less likely to occur. Li treated 53 cases of calcaneal fracture with incision reduction and internal fixation of the tarsal sinus, and the incidence of post-operative sural nerve injury was 9.6%<sup>19</sup>. The standard tarsal sinus incision is made below the anterior lateral malleolus, exposing the articular surface above the short and long peroneal tendons, where pulling the tendons downward may cause traction injury to the local sural nerve. Scholars conducted anatomical studies on the distribution of the sural nerve in 110 Korean carcasses, and the results showed that 58.8% of the carcasses had isolated a branch of the medial cutaneous nerve of the dorsal foot extending to the sural nerve within the standard tarsal sinus incision<sup>20</sup>. Therefore, a standard tarsal sinus incision may not be able to completely avoid sural nerve injury. A modified tarsal sinus incision can provide sufficient anatomical exposure to complete the reduction and fixation of calcaneal fractures. If it is necessary to extend back to the anterior process of the calcaneus, it will be easier to do so while protecting the long and short peroneal tendons, sural nerve, and accompanying blood vessels. The standard tarsal sinus incision makes it difficult to restore calcaneal width due to the limited exposure of the subtalar articular surface. A modified tarsal sinus incision can be used to reduce the fracture and fix the calcaneal fissure with a shapeable anatomical titanium plate. The location of the screw hole is determined percutaneously using the mold positioning method, after which the locking sleeve is placed. This avoids soft-tissue injury and reduces the possibility of injury to the lateral cutaneous nerve of the foot and subsequently obtains better biomechanical strength.

This study has the following limitations: the included sample size is small, and future studies with larger samples and multiple centers are needed to prove the efficacy of the presented approach. We did not report the effect of injury mechanisms and smoking history on surgical outcomes, which will serve as a limitation of this study and is expected to be explained in future studies. In addition, the researchers did not perform gait or plantar pressure distribution analyses; as such, it is uncertain whether there are significant abnormalities in post-operative gait patterns. Finally, this study did not compare the modified tarsal sinus incision with other surgical methods, and it is anticipated that future studies will be compared by statistical methods to highlight the advantages of the modified tarsal sinus incision.

## Conclusion

Despite the limitations of the current study, the modified tarsal sinus incision has shown to be one of the safe methods for the treatment of displaced intra-articular calcaneal fractures. The lateral hook curvy incision can fully expose the subtalar articular surface and the calcaneocuboid joint and avoid ineffective exposure and negative traction reduction, which is conducive to the reduction and healing of the fracture.

## Declarations

### *Ethics approval and consent to participate*

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Heze Bo'ai Hospital. Written informed consent was obtained from all participants in this study.

## Authors' contributions

Conception and design of the work: Fu CS and Wei BF; Data collection: Pei HJ, Xue CY, Zhou JJ, and Zhong GD; Supervision: Fu CS and Wei BF; Analysis and interpretation of the data: Fu CS, Wei BF, Pei HJ, Xue CY, Zhou JJ, and Zhong GD; Statistical analysis: Fu CS, Wei BF, Pei HJ, and Zhong GD; Drafting the manuscript: Fu CS and Wei BF; Critical revision of the manuscript: all authors; Approval of the final manuscript: all authors.

## Funding

The authors declare that they have not received funding.

## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

## References

1. Rammelt S, Zwipp H. Fractures of the calcaneus: current treatment strategies. *Acta Chir Orthop Traumatol Cech.* 2014;81:177-96.
2. Clare MP, Crawford WS. Managing complications of calcaneus fractures. *Foot Ankle Clin.* 2017;22:105-16.
3. Backes M, Schep NW, Luitse JS, Goslings JC, Schepers T. The effect of postoperative wound infections on functional outcome following intra-articular calcaneal fractures. *Arch Orthop Trauma Surg.* 2015;135:1045-52.
4. Backes M, Schepers T, Beerekamp MS, Luitse JS, Goslings JC, Schep NW. Wound infections following open reduction and internal fixation of calcaneal fractures with an extended lateral approach. *Int Orthop.* 2014;38:767-73.
5. Femino JE, Vaseenon T, Levin DA, Yian EH. Modification of the sinus tarsi approach for open reduction and plate fixation of intra-articular calcaneus fractures: the limits of proximal extension based upon the vascular anatomy of the lateral calcaneal artery. *Iowa Orthop J.* 2010;30:1612-7.
6. Budiman-Mak E, Conrad KJ, Roach KE. The foot function index: a measure of foot pain and disability. *J Clin Epidemiol.* 1991;44:561-70.
7. Gonzalez TA, Kwon JY. Sinus tarsi approach for calcaneus fractures. *Oper Tech Orthop.* 2015;25:235-41.
8. Schepers T. The sinus tarsi approach in displaced intra-articular calcaneal fractures: a systematic review. *Int Orthop.* 2011;35:697-703.
9. He K, Fu S, Liu S, Wang Z, Jin D. Comparisons in finite element analysis of minimally invasive, locking, and non-locking plates systems used in treating calcaneal fractures of sanders type II and type III. *Chin Med J (Engl).* 2014;127:3894-901.
10. Rao K, Dibbern K, Day M, Glass N, Marsh JL, Anderson DD. Correlation of fracture energy with sanders classification and post-traumatic osteoarthritis after displaced intra-articular calcaneus fractures. *J Orthop Trauma.* 2019;33:261-6.
11. Sanders R, Fortin P, DiPasquale T, Walling A. Operative treatment in 120 displaced intraarticular calcaneal fractures: results using a prognostic computed tomography scan classification. *Clin Orthop Relat Res.* 1993;290:87-95.
12. Schepers T, Backes M, Dingemans SA, De Jong VM, Luitse JS. Similar anatomical reduction and lower complication rates with the sinus tarsi approach compared with the extended lateral approach in displaced intra-articular calcaneal fractures. *J Orthop Trauma.* 2017;31:293-8.
13. Wei BF, Amendola A, Fu CS. *Clinical Anatomy and Surgical Atlas of the Foot and Ankle.* Jinan: Shandong Science and Technology Press Co Ltd.; 2021. p. 178-91.
14. Wei BF, Zhang JZ, Xu XY. *Surgical Anatomy Atlas of Foot and Ankle.* Beijing: People's Military Medical Press Co Ltd.; 2015. p. 187-91.
15. Jansen SC, Bransen J, Van Montfort G, Besselaar AT, Van der Veen AH. Should the extended lateral approach remain part of standard treatment in displaced intra-articular calcaneal fractures? *J Foot Ankle Surg.* 2018;57:1120-4.
16. Schepers T, Hartog DD, Vogels LM, Van Lieshout EM. Extended lateral approach for intra-articular calcaneal fractures: an inverse relationship between surgeon experience and wound complications. *J Foot Ankle Surg.* 2013;52:167-71.
17. Piovesana LG, Lopes HC, Pacca DM, Ninomiya AF, Dinato MC, Pagnano RG. Assessment of reproducibility of sanders classification for calcaneal fractures. *Acta Ortop Bras.* 2016;24:90-3.
18. De Groot R, Frima AJ, Schepers T, Roerdink WH. Complications following the extended lateral approach for calcaneal fractures do not influence mid-to long-term outcome. *Injury.* 2013;44:1596-600.
19. Li S. Wound and sural nerve complications of the sinus tarsi approach for calcaneus fractures. *Foot Ankle Int.* 2018;39:1106-12.
20. Jeon SK, Paik DJ, Hwang YI. Variations in sural nerve formation pattern and distribution on the dorsum of the foot. *Clin Anat.* 2017;30:525-32.



# Evaluation of hemostatic efficacy and safety of oxidized regenerated cellulose (Pahacel®) in coronary bypass surgery

## *Evaluación de la eficacia hemostática y de la seguridad de la celulosa regenerada oxidada (Pahacel®) en cirugía de bypass coronario*

Hasan A. Keskin

Department of Cardiovascular Surgery, Health Sciences University, Ankara Training and Research Hospital, Ankara, Turkey

### Abstract

**Objective:** The aim of this study is to evaluate the efficacy and safety of oxidized regenerated cellulose (ORC) in patients who underwent coronary artery bypass grafting (CABG) surgery and to compare the results of patients in whom ORC was used or not used for control of bleeding. **Method:** Pre-, intra-, and post-operative demographic and medical parameters of the patients in whom ORC was used or not used were compared. Quantitative data were analyzed with mean and standard deviation. Group differences were assessed with the Mann–Whitney U test. **Results:** It was found that the duration of surgery, average numbers of erythrocyte and fresh frozen plasma (FFP) transfusions during surgery, average post-operative FFP transfusion count, duration of intensive care unit stay, and chest tube removal times were lower in the ORC group compared to the control group, and all these differences were statistically significant ( $p < 0.05$  for all of these parameters). **Conclusions:** The study successfully demonstrated the effective and safe use of topical ORC in controlling bleeding and preventing oozing during CABG surgeries.

**Keywords:** Coronary artery bypass grafting. Oxidized regenerated cellulose. Complications. Hemostat. Hemostasis.

### Resumen

**Objetivo:** Evaluar la eficacia y la seguridad de la celulosa regenerada oxidada (CRO) en pacientes sometidos a cirugía de injerto de derivación de arteria coronaria y comparar los resultados de los pacientes en los que se utilizó o no la CRO para el control del sangrado. **Método:** Se compararon los parámetros demográficos y médicos pre-, intra- y posoperatorios de los pacientes en los que se utilizó o no CRO. Los datos cuantitativos se analizaron con media y desviación estándar. Las diferencias grupales se evaluaron con la prueba U de Mann Whitney. **Resultados:** Se encontró que la duración de la cirugía, el número promedio de transfusiones de eritrocitos y de plasma fresco congelado durante la cirugía, el recuento promedio de transfusiones de plasma fresco congelado posoperatorias, la duración de la estancia en la unidad de cuidados intensivos y los tiempos hasta la extracción del tubo torácico fueron menores en el grupo de CRO en comparación con el grupo control, y todas estas diferencias fueron estadísticamente significativas ( $p < 0.05$ ). **Conclusiones:** El estudio demostró con éxito el uso eficaz y seguro de la CRO tópica para controlar el sangrado y prevenir la supuración durante las cirugías de derivación de arteria coronaria.

**Palabras clave:** Cirugía de derivación de arteria coronaria. Celulosa regenerada oxidada. Complicaciones. Hemostático. Hemostasia.

### Correspondence:

Hasan A. Keskin

E-mail: attilakeskin@hotmail.com

Date of reception: 29-10-2023

Date of acceptance: 18-03-2024

DOI: 10.24875/CIRUE.M24000746

Cir Cir (Eng). 2024;92(5):605-612

Contents available at PubMed

www.cirugiaycirujanos.com

2444-0507/© 2024 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Bleeding is a common surgical complication which increases post-operative complications, unfavorable transfusion-related events, and the risk of infection, necessitating a longer hospital length of stay (LOS) and greater use of medical resources. When bleeding cannot be controlled during surgery using standard techniques, absorbable hemostatic agents (AHA) have been utilized as adjunctive therapy. When electrocoagulation, ligation, or other conventional techniques of bleeding control are ineffective or impractical, oxidized regenerated cellulose (ORC), a commonly used AHA, can be used in the control of small arterial, venous, and capillary hemorrhage<sup>1</sup>. ORC is a biodegradable, sterile, fibrous substance created by the oxidation of regenerated cellulose. Various forms of ORC are used in surgery for the control of bleeding as an absorbable hemostatic substance<sup>2</sup>. Despite the fact that ORC is widely used worldwide, research on issues relating to the safety and efficacy of this hemostat, as well as its effects on medical costs and surgical outcomes, has been ongoing for years. Many studies have examined its efficacy in numerous specialties, including urology, plastic surgery, obstetrics and gynecology, general surgery, neurology, and cardiovascular surgery<sup>3-7</sup>. Nevertheless, no studies other than two technical descriptions of the use of ORS in cardiac bypass procedures were found in the literature review<sup>8,9</sup>. Despite the fact that 345 coronary artery bypass grafting (CABG) surgeries used one of these techniques, the outcome factors assessed in that study were sparse and not provided in detail<sup>9</sup>.

The objective of the present investigation was to conduct a retrospective assessment of the effectiveness and safety of ORC in individuals who underwent coronary bypass surgery, specifically focusing on cases where this hemostatic agent was employed for bleeding control. In addition, the study aimed to compare these outcomes with those of patients in whom the hemostatic agent was not utilized. Numerous hemostatic products are used in medical practice, and the data obtained from this study can serve as a reference for researchers to compare the outcomes of different studies involving various hemostats. Positive findings from this study have the potential to generate interest among surgeons who have not yet utilized ORC in coronary bypass surgeries, encouraging them to use this product and to compare the efficacy and safety of ORC with other hemostats.

## Methods

This retrospective, cross-sectional, and observational research included patients who had undergone coronary bypass grafting surgery between September 2022 and March 2023 in the Cardiovascular Surgery Department of Health Sciences University Ankara Training and Research Hospital and in whom ORC was used or not used for control of bleeding. The study was approved by the Ethics Committee of Ankara Training and Research Hospital. The ORC product, used in this study was PAHACEL<sup>®</sup> standard absorbable hemostat, which is a Class III medical device, and manufactured by Altaylar Medikal, Ankara, Türkiye.

After pre-medication and induction of anesthesia, approximately 300-400 mL of blood was collected from all patients with hemoglobin levels above 12.0 for autotransfusion. All patients underwent the standard conventional cardiopulmonary bypass (CPB) technique. Autologous blood was intravenously administered to the patient after CPB. In the control group, conventional hemostasis was achieved and ORC was not applied. In patients in the ORC group, to ensure hemostasis, ORC product (PAHACEL<sup>®</sup>) was temporarily applied over the distal and proximal coronary bypass anastomoses, even if the bleeding was minimal, or there was oozing. Following the instructions in the product's user manual, the ORC product was removed once bleeding or leakage was controlled and was not left in the surgical area. After achieving hemostasis, three chest drainage tubes were inserted, one in the left hemithorax and two in the mediastinum. The sternum was approximated using four figure-of-eight wires, and the subcutaneous tissue was closed with PDS sutures, followed by skin closure using staples.

The evaluated parameters regarding the patients and the surgical procedures during the pre-operative, operative process, and post-operative hospital stay were age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, smoking status, additional diseases (diabetes mellitus, hypertension, chronic obstructive pulmonary disease [COPD], etc.), pre-operative thrombocyte, hematocrit, prothrombin time (PT) and pre-, intra-, and post-operative anti-clotting time (ACT) values, operation time, the number of per- and/or post-operative red blood cell or fresh frozen plasma (FFP) transfusions, post-operative platelet transfusion or fibrinogen treatment, the duration of post-operative intensive care

stay, post-operative hospital stay, amount of drainage into the chest tube, the time of chest tube removal, main complications, morbidity, and mortality.

Following standardized protocols, all patients who underwent surgery at the Cardiovascular Surgery Clinic for coronary artery disease were scheduled for a follow-up visit at the outpatient clinic on the 15<sup>th</sup> day after the operation for examination and removal of sutures were performed. In addition to this regular procedure, patients were informed upon discharge that if they experienced any unexpected signs or symptoms such as severe pain, redness, or discharge at the surgical site, high fever, or difficulty in breathing, they should promptly return to the hospital for immediate evaluation and care.

In line with these principles, during the standard follow-up visit on post-operative day 15 or when patients seek medical attention due to unexpected issues, their current complaints were assessed through questioning, and physical examinations were conducted. If a wound infection was suspected, the wound was drained, and a sample was collected for culture and antibiotic sensitivity testing. In cases where complications were suspected, appropriate tests were carried out and carefully evaluated.

The early complications identified for this study were obtained from patient records during their hospital stay and within the 1<sup>st</sup> month after the surgery. These complications included seroma, superficial and/or deep wound infections, hematoma, bleeding, tamponade, and pleural effusion. Retrieving information for this retrospective study posed no difficulties since all the parameters evaluated were routine and mandatory data recorded in the hospital's registry system by the attending physician.

Patients with pre-existing chronic liver or kidney dysfunction and those with missing recorded data were excluded from this retrospective analysis. All of the patients had been receiving acetylsalicylic acid preoperatively. Although it had a significant antiaggregant effect, this medication was not stopped, and the patients continued to receive the acetylsalicylic acid treatment.

## Results

The study compared a control group of 40 patients, aged  $61.05 \pm 9.12$  (range, 33-78 years), with a group of 52 patients who underwent hemostasis using ORC (ORC group), with an average age of  $62.56 \pm 9.29$  (range, 44-83 years). Table 1 presents the demographic,

medical, and pre-operative hematological profiles of the patients. The groups were similar in terms of age, gender, BMI, ASA scores, smoking habits, and most comorbid diseases, except for COPD, as well as pre-operative PT, platelet count, hematocrit, and ACT values. The mean number of vascular grafts was comparable between the control and ORC groups ( $3.35 \pm 1.07$  and  $3.25 \pm 0.91$ , respectively,  $p > 0.05$ ). All patients in both groups had an ASA III score.

Table 2 outlines the intraoperative parameters. There was a statistically significant difference in the average duration of the operation between the control group ( $289.17 \pm 50.62$  min) and the ORC group ( $265.13 \pm 59.45$  min) ( $p < 0.05$ ). The ORC group had significantly fewer erythrocyte and FFP transfusions compared to the control group ( $p < 0.05$ ). The mean duration of cardiopulmonary bypass and ACT values did not differ significantly between the groups ( $p > 0.05$ ). LIMA was consistently used as a graft in both groups, with the most common number of grafts being three.

Post-operative parameters in table 3 revealed that in the ORC group, there were significantly fewer FFP transfusions, a shorter mean follow-up time in the intensive care unit, and a shorter mean chest tube removal time compared to the control group ( $p < 0.05$ ). While there was no statistical difference in the total amount of drainage to the chest tube ( $p > 0.05$ ), the mean total drainage was less in the ORC group ( $1067.31 \pm 528.58$  mL) than in the control group ( $1115.00 \pm 465.36$  mL). ACT, activated partial thromboplastin time, and the mean number of erythrocyte transfusions did not differ significantly between the groups ( $p > 0.05$ ). Although the mean duration of post-operative hospital stay was shorter in the ORC group, there was no significant difference between the groups ( $p > 0.05$ ). Only one patient in the ORC group required a platelet transfusion, and no patients in either group received fibrinogen supplementation.

In the ORC group, eight complications occurred in seven patients, including 3 cases of atrial fibrillation (7.3%), 3 cases of superficial wound infection (7.3%), and 2 cases of pleural effusion (4.9%). The control group experienced 2 sternal wound infections (5.0%) and 4 pleural effusions (10.0%). All complications were effectively addressed during the initial hospitalization period and none of the patients required readmission.

Two patients (3.8%) in ORC and 1 patient (2.5%) in control group required reoperation due to excessive bleeding, which was defined as bleeding exceeding

**Table 1. The demographic and medical features and pre-operative hematological profile of the patients**

Parameters	Control (n = 40)	ORC group (n = 52)
Age (years) (mean $\pm$ SD)	61.05 $\pm$ 9.12	62.56 $\pm$ 9.29
Gender (number/percentage)		
Male	31 (77.5%)	41 (78.8%)
Female	9 (22.5%)	11 (21.2%)
BMI (kg/m <sup>2</sup> ) (mean $\pm$ SD)	28.05 $\pm$ 4.19	28.16 $\pm$ 4.73
ASA scores (number/percentage)		
ASA 1	-	-
ASA 2	-	-
ASA 3	40 (100%)	52 (100%)
ASA 4	-	-
Smokers (number/percentage)	12 (30.0%)	13 (25.0%)
Comorbidities (number/percentage)		
HT	23 (57.5%)	32 (61.5%)
DM	24 (60.0%)	30 (57.7%)
COPD	1 (2.5%)	8 (15.4%)
Others	1 (2.5%)	3 (5.7%)
Prothrombin time (s) (mean $\pm$ SD)	12.79 $\pm$ 1.76	13.72 $\pm$ 1.08
Platelet count ( $\times 10^3/\mu\text{L}$ ) (mean $\pm$ SD)	271.56 $\pm$ 56.62	263.96 $\pm$ 69.20
Hematocrit (%)	41.01 $\pm$ 5.74	40.59 $\pm$ 6.47
ACT (s)	135.29 $\pm$ 20.09	139.91 $\pm$ 20.08

No difference was found between the groups for all parameters ( $p > 0.05$ ); ASA: American Society of Anesthesiologists; BMI: body mass index; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; HT: hypertension; ACT: activated clotting time; SD: standard deviation; ORC: oxidized regenerated cellulose.

**Table 2. Pre-operative parameters of the patients**

Parameters	Control (n = 40)	ORC group (n = 52)
Operation time (min) (mean $\pm$ SD)*	289.17 $\pm$ 50.62	265.13 $\pm$ 59.45
Duration of cardiopulmonary bypass (min)	51.20 $\pm$ 14.82	48.64 $\pm$ 18.50
Mean number of vascular grafts	3.35 $\pm$ 1.07	3.25 $\pm$ 0.91
Erythrocyte transfusions (mean $\pm$ SD)*	0.38 $\pm$ 0.16	0.02 $\pm$ 0.01
FFP transfusions* (mean $\pm$ SD)	0.40 $\pm$ 0.16	0.27 $\pm$ 0.12
ACT (s $\pm$ SD)	749.54 $\pm$ 157.57	709.77 $\pm$ 157.26

\*Statistically different,  $p < 0.05$ . FFP: fresh frozen plasma; ACT: activated clotting time; s: seconds; SD: standard deviation; ORC: oxidized regenerated cellulose.

200 cc/h during the early post-operative period. Both patients experienced 200 cc/h bleeding over a period of 5 h, leading to the decision for emergent reoperation. Surgical intervention was performed to achieve local hemostasis since the patients had active surgical bleeding (not oozing) that could not be controlled using hemostatic agents. It was concluded that these two cases of hemorrhage requiring reoperation were not directly associated with the evaluation of ORC's efficacy and safety, which were the aim of the current

study. Therefore, these reoperations were not considered in the "discussion" part.

No mortality was observed in the current study.

The Statistical Package for the Social Sciences (SPSS) version 25 (SPSS Inc., Chicago, USA) program was used for statistical analysis. For quantitative data such as age and length of hospital stay, the mean and standard deviation values were used to determine the measure of central trends. Frequency tables and charts were used to present estimated rates of

**Table 3. Post-operative parameters of the patients**

Parameters	Control (n = 40)	ORC group (n = 52)
Erythrocyte transfusions (mean $\pm$ SD)	1.90 $\pm$ 1.06	1.71 $\pm$ 1.05
FFP transfusions (mean $\pm$ SD)*	1.65 $\pm$ 1.12	1.23 $\pm$ 1.18
Platelet transfusion (number of patients/number of transfused platelet suspension)	0/0	1/1
Fibrinogen supplementation (number of patients/number of transfused fibrinogen suspension)	0/0	0/0
ACT (s $\pm$ SD)	119.19 $\pm$ 11.64	121.63 $\pm$ 13.64
aPTT (s $\pm$ SD)	30.50 $\pm$ 6.31	28.25 $\pm$ 2.73
Follow-up time in intensive care unit (h $\pm$ SD)*	102.15 $\pm$ 36.79	90.19 $\pm$ 45.67
Post-operative hospital stay (days $\pm$ SD)	12.54 $\pm$ 6.83	10.75 $\pm$ 6.86
Total amount of drainage to chest tube (mL $\pm$ SD)	1115.00 $\pm$ 465.36	1067.31 $\pm$ 528.58
Chest tube removal time (h $\pm$ SD)*	94.45 $\pm$ 37.88	52.29 $\pm$ 46.74
Post-operative early complications (number of patients)		
Atrial fibrillation	0 (0%)	3 (5.7%)
Superficial wound infection	0 (0%)	3 (5.7%)
Sternal wound infections	2 (5.0%)	0 (0%)
Reoperation for bleeding	1 (2.5%)	2 (3.8%)
Cardiac tamponade	0 (0%)	0 (0%)
Pleural effusion	4 (10.0%)	3 (5.7%)

\*Statistically different,  $p < 0.05$ . FFP: fresh frozen plasma; ACT: activated clotting time; s: seconds; h: hours; SD: standard deviation; ORC: oxidized regenerated cellulose; aPTT: activated partial thromboplastin time.

qualitative data such as gender and rate of complications. To determine whether there was a difference between the experimental and control groups, it was examined whether the difference between the groups was significant. In this context, since parametric test assumptions were not met, this difference was examined with the Mann–Whitney U test, which is one of the non-parametric tests for the comparison of groups.

## Discussion

The disproportion between the blood supply of the myocardium through coronary vessels and the oxygen need of the myocardium leads to ischemic heart disease<sup>10</sup>. Annually, more than 200,000 CABG procedures are carried out in the United States. CABG surgery is frequently regarded as a high-risk procedure with high 30-day morbidity (up to 14.0%) and mortality (up to 2.0%) rates<sup>11</sup>. In the current study, there were no instances of mortality (0%). The morbidity rates, at 15% for the control group and 15.4% for the ORC group, align with existing literature. While the recent adoption of early extubation and fast-track protocols has generally resulted in shorter hospital stays,

averaging 5.4 days postoperatively<sup>11</sup>, in the current research, longer post-operative LOS, with 12.54  $\pm$  6.83 days for the control group and 10.75  $\pm$  6.86 days for the ORC group, were found. Following CABG surgery, a large number of patients commonly require hospital readmissions (approximately 14%) and emergency department visits (additional 10%) within 30 days after discharge, frequently for complications or complaints linked to the surgery. In all, 7% of patients who have had CABG surgery will require more than one readmission or emergency department visit within 30 days following the procedure<sup>11</sup>. Every complication identified in the present study was successfully addressed during the initial hospitalization period, and there was no necessity for patients to be readmitted after discharge.

Several risk factors contribute to perioperative morbidity and mortality in CABG surgery. Post-operative bleeding is a common complication, impacting approximately 10% of patients and leading to adverse outcomes and higher costs. Definitions of “excessive” bleeding vary but are often based on chest tube drainage. Age, complex operations, pre-operative anemia, cardiac function, cardiopulmonary bypass time, male



sex, and lower BMI contribute to the risk of excessive bleeding, emphasizing the importance of careful management of post-operative bleeding due to its association with increased mortality risk. The risk of bleeding is also associated with surgeon-specific factors such as attention to hemostasis. Pre-operative dual antiplatelet medication (acetylsalicylic acid and clopidogrel, ticagrelor, or prasugrel) may have an approximately 15% risk of bleeding. Although guidelines advise to stop dual antiplatelet treatment 5 days before surgery, this is frequently impossible in emergent operations<sup>12</sup>. In the present study, although all of the patients had been receiving acetylsalicylic acid, which had a significant antiaggregant effect in the pre-operative period, only 2 patients (3.9%) in ORC group and 1 patient (2.5%) had reoperation for bleeding.

Post-operative bleeding, often linked to antiplatelet or anticoagulant use in CABG surgery, remains a constant concern for surgeons. Persistent bleeding from mediastinal drains can lead to sudden cardiopulmonary instability, particularly acute pericardial tamponade, resulting in death. While various sources contribute to bleeding after CABG, oozing from anastomotic suture lines is a primary cause, requiring prompt surgical exploration to prevent adverse outcomes<sup>12</sup>.

Traditional surgical methods such as ligation and cauterization may sometimes fail to control bleeding, prompting the use of alternative approaches. Topical hemostatic agents, including ORC, offer a solution. ORC, composed of structured cellulose, stands out for its bioabsorption, biocompatibility, and ease of use. It activates the intrinsic coagulation pathway, forms a gel-like layer, and induces vasoconstriction. ORC's versatility makes it suitable for various surgical sites, ensuring quick adaptation and effective management of local bleeding<sup>1,2,13</sup>. Although ORC is widely used in many surgical fields worldwide, there are only two technical descriptions of the use of ORC in coronary artery bypass surgeries<sup>8,9</sup>.

Di Lello et al.<sup>8</sup> employed ORC for sutureless fixation of long aortocoronary saphenous vein grafts (SVG), tailoring an appropriate-sized ORC sheet over the graft segment. While their aim differed from the current study, focusing on graft fixation rather than hemostasis, the technique showcased ORC's versatility.

Canver<sup>9</sup> introduced a method to reduce fatal complications in myocardial revascularization, covering the internal thoracic artery pedicle, distal anastomosis, and SVGs with ORC pieces. Liquid thrombin

prevented dislodging, and the chest was closed while monitoring bleeding through flexible suction catheters. In 345 consecutive CABG procedures using this technique, only 0.57% required re-exploration for early post-operative bleeding. No instances of cardiopulmonary collapse or long-term complications were reported, suggesting ORC application might prevent post-operative bleeding and acute graft kinking effectively.

In my opinion, the main limitation of the previous study was the evaluation of a very limited number of outcome parameters, despite the inclusion of a large number of patients. In addition, no other research studies were found in the literature utilizing the same hemostasis technique, suggesting that the results of the study may not have been deemed satisfactory by other researchers. In contrast, the present study evaluated a significant number of outcome parameters. Another difference between the previous study and the current study is that while the previous study applied a liquid thrombin spray on ORC, such an application was not performed in the present study. The final and significant difference of the current study from the previous one is the presence of a control group in the current study.

Given the limited number of studies assessing the hemostatic effects of ORC in CABG surgery, the author conducted the current comparative retrospective analysis. The aim was to compare the pre-, intra-, and post-operative data of patients in whom ORC was used for enhanced hemostasis with those who did not receive any hemostatic agent during CABG surgeries. In summary, when considering various parameters between two groups that exhibited similarities in demographic and medical features, pre-operative hematological profiles, and the number of vascular grafts applied, it was found that the duration of surgery, average numbers of erythrocyte and FFP transfusions during surgery, average post-operative FFP transfusion count, duration of intensive care unit stay, and chest tube removal times were lower in the ORC group compared to the control group, and all these differences were statistically significant. On the other hand, although statistically significant differences were not found, it is noteworthy that the post-operative hospital stay and the total amount of drainage to the chest tube were lower in the ORC group compared to the control group. Given that all these parameters with different values between the groups could be directly or indirectly associated with the patient's hemostatic success and bleeding status, these differences were

interpreted as indicative of the positive contributions of ORC use to hemostasis.

Although some other hemostatic agents such as fibrin sealant<sup>13</sup> and tranexamic acid<sup>14</sup> were used successfully in patients undergoing CABG surgery, there was no studies comparing the effects of these hemostats with ORC in CABG surgeries.

While ORC is widely used and effective, there have been reported adverse effects. In a rare case, ORC residue caused a post-traumatic bronchobiliary fistula, attributed to ORC erosion and diaphragmatic migration<sup>15</sup>. Another case involved a child with pelvic neuroblastoma, where ORC, used for hemostasis, led to a mass mimicking tumor recurrence. Pathological evaluation revealed fibrotic tissue with giant cells, prompting caution about minimizing topical hemostat use and avoiding retention unless essential<sup>16</sup>. Despite ORC's biocompatibility, insufficient absorption can trigger foreign body reactions, mimicking various conditions such as tumor recurrence, granuloma, or abscess<sup>2</sup>. An adverse event occurred with oxidized cellulose (OC) combined with epsilon aminocaproic acid (EACA), leading to acute ischemia. *In vitro* experiments revealed OC's rigid structure in EACA, prompting a cautionary note against their combined use<sup>17</sup>.

In addition to these undesirable effects, seroma, allergic skin reactions, or in some cases, abscess formations may develop with the use of ORC<sup>2</sup>. In addition to a case series<sup>18</sup> reporting subhepatic mass formation (five out of 83 patients) after laparoscopic cholecystectomy operations, there are also studies reporting that the use of ORC increases the risk of rehospitalization<sup>19</sup>.

## Conclusion

The findings of the current study, which utilized topical ORC to achieve hemostasis and prevent oozing at anastomotic sites in CABG surgeries, demonstrated the effective and safe use of ORC with low complication rates. A key aspect of this approach was the removal of ORC after achieving hemostasis, in accordance with the usage guidelines. Although some literature reports have highlighted potential adverse effects associated with ORC usage, none of these effects have been deemed significant enough to hinder the use of ORC. Moreover, the technique described in this manuscript can effectively mitigate most of these undesired adverse events. Conducting studies that compare the

outcomes of patients undergoing CABG surgery with or without the use of ORC, along with studies involving a larger number of patients, would provide valuable guidance for surgeons regarding the safety and effectiveness of ORC in achieving hemostasis in these surgeries. In addition, studies comparing ORC with other hemostatic agents in terms of hemostatic success in CABG procedures would contribute to a better understanding of the efficacy and safety of these products.

## Acknowledgments

The author thanks Professor Dr. Kemal Kismet and Dr. Kemal Tekin for their dedication and contributions during the preparation of this study.

## Funding

The author declares that he has not received funding.

## Conflicts of interest

The author declares no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The author declares that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The author declares that they he has followed the protocols of his work center on the publication of patient data.

**Right to privacy and informed consent.** The author has obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

**Use of artificial intelligence for generating text.** The author declares that he has not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

## References

1. Qian Z, Xiong F, Xia X, Gu P, Wang Q, Wu A, et al. Clinical and economic impact of oxidized regenerated cellulose for surgeries in a Chinese tertiary care hospital. *J Comp Eff Res.* 2020;9:1079-90.
2. Franceschini G. Internal surgical use of biodegradable carbohydrate polymers. Warning for a conscious and proper use of oxidized regenerated cellulose. *Carbohydr Polym.* 2019;216:213-6.

3. Shetty DP, Nair HC, Shetty V, Punnen J. A novel treatment for pulmonary hemorrhage during thromboendarterectomy surgery. *Ann Thorac Surg.* 2015;99:77-8.
4. Keshavarzi S, MacDougall M, Lulic D, Kasasbeh A, Levy M. Clinical experience with the Surgicel family of absorbable hemostats (oxidized regenerated cellulose) in neurosurgical applications: a review. *Wounds.* 2013;25:160-7.
5. Portilla D, Hernández-Giraldo C, Moreno B, Quijano F, Hoyos LR, Angarita AM, et al. A local hemostatic agent for the management of postpartum hemorrhage due to placenta previa and placenta accreta: a cross-sectional study. *Arch Gynecol Obstet.* 2013;288:543-9.
6. Morelli L, Morelli J, Palmeri M, D'Isidoro C, Kauffmann EF, Tartaglia D, et al. Robotic surgery and hemostatic agents in partial nephrectomy: a high rate of success without vascular clamping. *J Robot Surg.* 2015;9:215-22.
7. Sabel M, Stummer W. The use of local agents: surgicel and Surgifoam. *Eur Spine J.* 2004;13:S97-101.
8. Di Lello F, Mullen DC, Flemma RJ. Sutureless fixation of long aortocoronary saphenous vein grafts with oxidized regenerated cellulose. *Ann Thorac Surg.* 1989;47:473-4.
9. Canver CC. A draping technique for prevention of coronary bypass graft kinking and suture-line oozing. *J Card Surg.* 1996;11:408-10.
10. Straus S, Haxhibeqiri-Karabdic I, Grabovica SG, Granov N. A difference in bleeding and use of blood and blood products in patients who were preoperatively on aspirin or dual antiplatelet therapy before coronary artery bypass grafting. *Med Arch.* 2018;72:31-5.
11. Montrief T, Koyfman A, Long B. Coronary artery bypass graft surgery complications: a review for emergency clinicians. *Am J Emerg Med.* 2018;36:2289-97.
12. Stephens RS, Whitman GJ. Postoperative critical care of the adult cardiac surgical patient: part II: procedure-specific considerations, management of complications, and quality improvement. *Crit Care Med.* 2015;43:1995-2014.
13. Wan Y, Lim S, Gao X, Danker WA 3<sup>rd</sup>, Kocharian R, Gangoli G, et al. Bleeding-related complications and readmission rates associated with fibrin sealant use in patients undergoing coronary artery bypass graft surgery in the United States. *J Cardiothorac Vasc Anesth.* 2017;31:876-82.
14. De Bonis M, Cavaliere F, Alessandrini F, Lapenna E, Santarelli F, Moscato U, et al. Topical use of tranexamic acid in coronary artery bypass operations: a double-blind, prospective, randomized, placebo-controlled study. *J Thorac Cardiovasc Surg.* 2000;119:575-80.
15. Seyed-Alagheband SA, Shahmoradi MK, Shekouhi R. Posttraumatic bronchobiliary fistulae due to foreign body remnants after a road traffic injury: a case report. *J Med Case Rep.* 2021;15:291.
16. Turkyilmaz Z, Karabulut R, Kaya C, Gokce D, Kolay E, Sonmez K. Surgicel mimicking recurrent pelvic neuroblastoma in a 3-year-old boy. *Acta Chir Belg.* 2022;122:266-8.
17. Alvarez JB, Quiroga JS, Cereijo JM, Lopez LR. Oxidized cellulose as the cause of an acute ischemic event after coronary revascularization. *Interact Cardiovasc Thorac Surg.* 2010; 11:488-9.
18. Spaziani E, Di Filippo A, Francioni P, Spaziani M, De Cesare A, Picchio M. Subhepatic mass occurrence after using oxidized and regenerated cellulose polymer in laparoscopic cholecystectomy: a case series. *Acta Chir Belg.* 2018;118:48-51.
19. Arisheh MA, Venturero M, Froom P. Oxidized regenerated cellulose during laparoscopic cholecystectomy increases the risk of rehospitalization. *Am Surg.* 2020;86:386-8.

# Acute kidney injury and mortality in patients with critical COVID-19 in Mexico: case-control study

*Lesión renal aguda y mortalidad en pacientes con COVID-19 grave en México: estudio de casos y controles*

Ivette Mata-Maqueda<sup>1,2</sup>, Juan C. Solís-Sáinz<sup>2</sup>, Guadalupe Zaldivar-Lelo de Larrea<sup>2</sup>, Ernesto Deloya-Tomas<sup>1,2,3</sup>, Jorge López-Fermin<sup>1,2,3</sup>, M<sup>a</sup> Guadalupe Olvera-Ramos<sup>1,2,3</sup>, Gabriela Castillo-Gutiérrez<sup>1,2,3</sup>, Jorge D. Carrión-Moya<sup>1,2,3</sup>, and Orlando R. Pérez-Nieto<sup>1,2,3\*</sup>

<sup>1</sup>Health Services of the State of Queretaro; <sup>2</sup>School of Medicine, Autonomous University of Queretaro; <sup>3</sup>Intensive Care Unit, General Hospital of San Juan del Río, Queretaro, Mexico

## Abstract

**Objective:** We aimed to test the association between acute kidney injury (AKI) and mortality in critically ill patients with Coronavirus disease 2019 (COVID-19). **Method:** We conducted a single-center case-control study at the intensive care unit (ICU) of a second-level hospital in Mexico. We included 100 patients with critical COVID-19 from January to December 2021, and collected demographic characteristics, comorbidities, APACHE II, SOFA, NEWS2, and CO-RADS scores at admission, incidence of intrahospital complications, length of hospital and ICU stay, and duration of mechanical ventilation, among others. **Results:** The median survival of deceased patients was 20 days. After multivariable logistic regression, the following variables were significantly associated to mortality: AKI (adjusted odds ratio [AOR] 6.64, 95% confidence intervals [CI] = 2.1-20.6,  $p = 0.001$ ), age > 55 years (AOR 5.3, 95% CI = 1.5-18.1,  $p = 0.007$ ), and arrhythmias (AOR 5.15, 95% CI = 1.3-19.2,  $p = 0.015$ ). Median survival was shorter in patients with AKI (15 vs. 22 days,  $p = 0.043$ ), as well as in patients with overweight/obesity (15 vs. 25 days,  $p = 0.026$ ). **Conclusions:** Our findings show that the development of AKI was the main risk factor associated with mortality in critical COVID-19 patients, while other factors such as older age and cardiac arrhythmias were also associated with this outcome. The management of patients with COVID-19 should include renal function screening and staging on admission to the Emergency Department.

**Keywords:** Coronavirus disease 2019. Severe acute respiratory syndrome coronavirus 2. Acute kidney injury. Mortality. Risk factors.

## Resumen

**Objetivo:** Probar la asociación entre lesión renal aguda y mortalidad en pacientes con COVID-19 grave. **Método:** Realizamos un estudio de casos y controles unicéntrico en la unidad de cuidados intensivos (UCI) de un hospital de segundo nivel en México. Incluimos 100 pacientes con COVID-19 grave de enero a diciembre 2021, recolectando características demográficas, comorbilidad, APACHE II, SOFA, NEWS2 y CO-RADS al ingreso, incidencia de complicaciones intrahospitalarias, duración de la estancia hospitalaria y en la UCI, duración de ventilación mecánica, etc. **Resultados:** La mediana de supervivencia de los pacientes que fallecieron fue de 20 días. Al realizar el análisis de regresión logística multivariable, las siguientes variables se asociaron significativamente con la mortalidad: lesión renal aguda (odds ratio ajustada [ORA]: 6.64; intervalo de confianza

### \*Correspondence:

Orlando R. Pérez-Nieto  
E-mail: orlando\_rpn@hotmail.com  
2444-0507/© 2023 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Date of reception: 25-04-2023  
Date of acceptance: 25-10-2023  
DOI: 10.24875/CIRUE.M23000747

Cir Cir (Eng). 2024;92(5):613-619  
Contents available at PubMed  
[www.cirugiaycirujanos.com](http://www.cirugiaycirujanos.com)

del 95% [IC95%]: 2.1-20.6;  $p = 0.001$ ), edad > 55 años (ORa: 5.3; IC95%: 1.5-18.1;  $p = 0.007$ ) y arritmias (ORa: 5.15; IC95%: 1.3-19.2;  $p = 0.015$ ). La supervivencia fue menor en pacientes con lesión renal aguda (15 vs. 22 días;  $p = 0.043$ ), así como en pacientes con sobrepeso u obesidad (15 vs. 25 días;  $p = 0.026$ ). **Conclusiones:** Nuestros resultados muestran que el desarrollo de lesión renal aguda es el principal factor de riesgo asociado a mortalidad en pacientes con COVID-19 grave, mientras que otros factores, como la edad > 55 años y la presencia de arritmias cardíacas, también se asocian a mortalidad por COVID-19. El manejo de pacientes con COVID-19 debe incluir el tamizaje y la estadificación de la función renal al ingreso a urgencias.

**Palabras clave:** COVID-19. SARS-CoV-2. Lesión renal aguda. Mortalidad. Factores de riesgo.

## Introduction

Coronavirus disease 2019 (COVID-19) is an acute respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was declared a global pandemic on March 11, 2020. As of April 19, 2023, more than 6.9 million deaths have been reported worldwide<sup>1</sup>. This virus mainly affects the respiratory system, producing fever, cough, headache, shortness of breath, sore throat, and chest pain<sup>2</sup>. Nevertheless, it may also cause acute respiratory distress syndrome (ARDS) and multiple organ dysfunction among other severe manifestations of disease. In this regard, acute kidney injury (AKI) has been described as a severe complication of COVID-19, with an incidence ranging from 4.5% and 28%, and a higher prevalence in patients hospitalized in the intensive care unit (ICU)<sup>2,3</sup>. The mechanisms that promote kidney disease have been related to damage induced by cytokines, systemic effects related to mechanical ventilation, and ARDS<sup>4</sup>.

AKI is known to increase the severity of illness, duration of hospitalization, and mortality in COVID-19 patients<sup>5</sup>. In fact, AKI has been described as an independent risk factor for mortality in COVID-19 patients hospitalized in the ICU<sup>6</sup>. However, information on kidney disease in patients with COVID-19 is still limited, as the majority of published studies in this respect are case reports and case series<sup>5</sup>. Furthermore, little is known concerning the relationship between AKI and COVID-19 in Hispanic populations, in whom risk factors for disease progression, adverse outcomes, and death from COVID-19 are especially prevalent<sup>7-9</sup>.

For the above reasons, in this study, we aimed to test the association between AKI and mortality in critically ill patients with COVID-19 in the ICU of a second-level public hospital in Mexico.

## Materials and methods

### Setting and patients

We conducted a single-center case-control study at the ICU of the Hospital General de San Juan del Río, part of the Health Services of the State of Querétaro, Mexico (SESEQ), from January to December 2021. Inclusion criteria were all patients with critical COVID-19 (according to the World Health Organization severity definitions<sup>10</sup>) admitted to the ICU during the entire study period. Exclusion criteria were incomplete or missing medical records and patients who were transferred to another medical unit. Consecutive convenience sampling of patients was performed.

In this study, the ethical precepts of the Declaration of Helsinki were followed, and the study protocol was approved in July 2020 by the Research Committee of SESEQ, with the registration number 1201/Subdirección de Enseñanza, Programa de Investigación en Salud/31-07-2020.

The primary outcome was mortality; hence, cases were defined as patients who died in the ICU, while controls as patients who survived until discharge. Exposures were defined as sex, age, history of comorbidities, APACHE II, SOFA, NEWS2, and CO-RADS scores at ICU admission, the incidence of intrahospital complications (AKI, arrhythmias, and secondary infections), length of hospital and ICU stay, duration of mechanical ventilation, patient-ventilator asynchrony, PaO<sub>2</sub> levels, and static pulmonary compliance. Data were collected by Critical Care Medicine resident physicians and attendings through a review of patients' medical records.

### Statistical analysis

Sample size calculations were performed based on the mortality risk by AKI in COVID-19 patients.

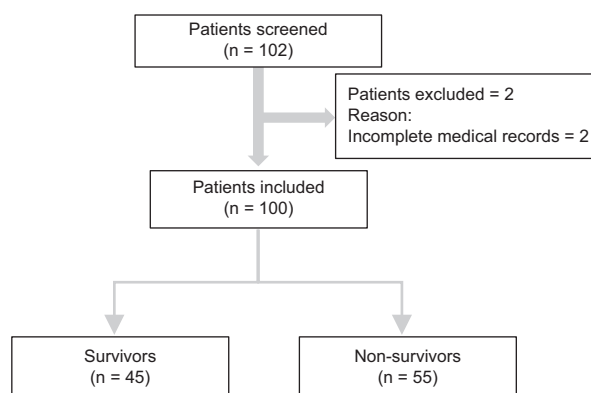


Assuming a relative risk of 3.08<sup>11</sup>, and a mortality rate of 47%<sup>2</sup>, we estimated a minimum of 33 individuals, with an 80% power and alpha of 0.05, allowing for a loss of 20%.

Descriptive statistics were used in qualitative variables. Continuous and categorical variables are presented as means, standard deviations, frequencies, and percentages, where applicable. Differences between categorical variables were evaluated by Fisher's exact test and by analysis of variance for continuous variables. Statistical significance was defined as  $p < 0.05$ . Normality in the distribution of the variables was tested by the Kolmogorov–Smirnov test. The Mann–Whitney and Kruskal–Wallis tests were used to evaluate the difference between medians, as well as Spearman's one-tailed correlation test for all the non-normally distributed data. Kaplan–Meier analyses were performed to assess survival. Both bivariable and multivariable binary logistic regression analyses were used to identify factors associated with the mortality. Variables with a  $p < 0.05$  in the bivariable analysis were fitted into the multivariable logistic regression analysis. Both crude odds ratio and adjusted odds ratio with their corresponding 95% Confidence intervals were calculated to show the strength of the association. In multivariable analysis, variables with a  $p < 0.05$  were considered as statistically significant. The fitness of the model was checked by using the Hosmer–Lemeshow goodness-of-fit test. All analyses and figures were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, N.Y., USA) and PRISM Software (GraphPad Prism v. 8), respectively.

## Results

One hundred and twenty-two potentially eligible patients were screened. After the application of inclusion and exclusion criteria, 100 patients were included in the final analyses (Fig. 1). Table 1 shows the general characteristics of our study population. Fifty patients were male and the mean age was 49 years. Obesity was the most frequent comorbidity ( $n = 44$ , 44%). Median APACHE II, SOFA, NEWS2 and CORADS scores at admission were 15, 9, 9, and 5, respectively. The incidence of intrahospital complications such as AKI, arrhythmia, ventilator-associated pneumonia, and catheter-related urinary tract infections were 56%, 70%, 67%, and 10%, respectively.



**Figure 1.** Patient inclusion flowchart and reasons for exclusion.

**Table 1.** General characteristics of our population

Variable	Total sample (n = 100)
Sex*	
Male	50 (50)
Female	50 (50)
Age** (years)	
Male	49.1 (12.2)
Female	49.4 (14.4)
Comorbidities*	
None	22 (22)
Obesity	44 (44)
Overweight	11 (11)
Hypertension	38 (38)
Diabetes mellitus	30 (30)
Patients with two or more comorbidities	35 (35)
Scores***	
APACHE II	15 (12-20)
SOFA	9 (7-11)
NEWS2	9 (7-11)
CORADS	5 (5-5)
Intrahospital complications*	
Acute kidney injury	56 (56)
Arrhythmias (all ventricular extrasystoles)	70 (70)
Ventilator-associated pneumonia	67 (67)
Catheter-related UTI	10 (10)
Days of hospital stay***	14 (10.75-23.25)
Days in ICU***	11 (6-20)
Days on mechanical ventilation***	9 (5-17)
Patient-ventilator asynchrony*	49 (49)
PaO <sub>2</sub> (mmHg)**	63.4 (11.4)
Static pulmonary compliance***	23 (18-26)
Mortality*	55 (55)

\*Frequency, (percentage). \*\*Mean, (standard deviation). \*\*\*Median, (25<sup>th</sup>-75<sup>th</sup> percentiles). ICU: intensive care unit; PaO<sub>2</sub>: arterial partial pressure of oxygen; UTI: urinary tract infection.

The median ICU stay was 11 days (interquartile range [IQR] ± 14), while the median days on mechanical ventilation were 9 (IQR ± 12). The mortality rate in our population was 55% ( $n = 55$ ).

In the bivariable logistic regression, the variables AKI, APACHE score > 25, age > 55, arrhythmias, overweight and obesity, and male sex were positively associated with mortality. However, when the multivariable logistic regression was employed only AKI (AOR 6.64, 95% CI 2.14-20.62,  $p = 0.001$ ), age > 55 years (AOR 5.3, 95% CI 1.57-18.15,  $p = 0.007$ ), and arrhythmia (AOR 5.15, 95% CI 1.37-19.27,  $p = 0.015$ ) were significantly associated with mortality (Table 2).

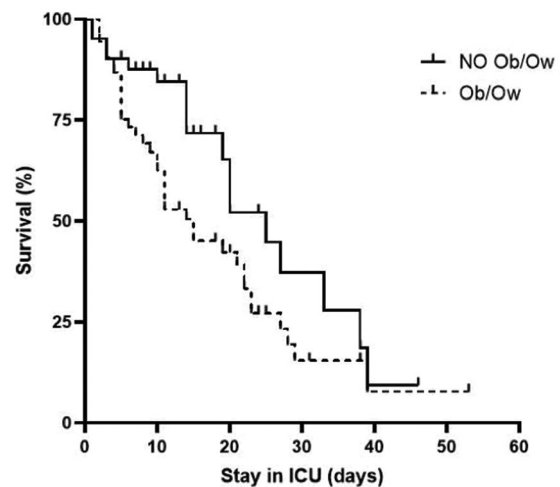
On the other hand, age was significantly higher in deceased patients, compared to survivors (52.9 vs. 44.9 years, using Student's  $t$ -test,  $p = 0.0014$ ; data not shown). Similarly, APACHE II scores were also higher in the non-survivor group, compared to survivors (16 vs. 14, using Mann-Whitney test,  $p = 0.032$ ; data not shown). In addition, the length of mechanical ventilation was also higher in deceased patients, compared to non-deceased (11 vs. 8 days, using the Mann-Whitney test,  $p = 0.032$ ; data not shown).

There were no significant differences in the SOFA and NEWS2 scores, length of hospital and ICU stay, number of comorbidities,  $\text{PaO}_2$  levels, and static pulmonary compliance between survivors and non-survivors (data not shown). Similarly, there was no correlation between age and length of ICU stay ( $p = 0.18$ , Spearman's correlation test; data not shown).

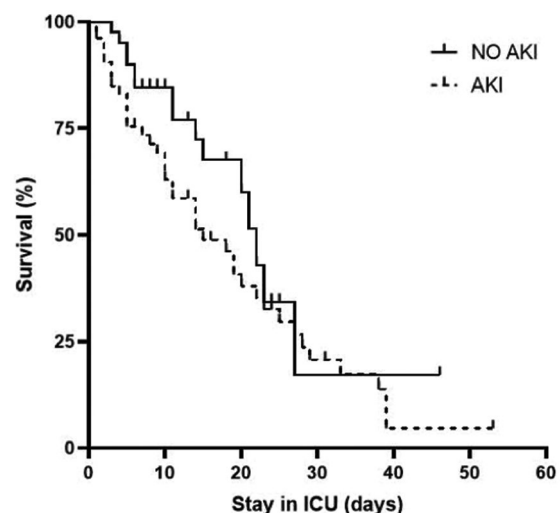
Concerning the deceased patients, the global median survival was 20 days. When comparing the survival of deceased patients with and without overweight and obesity, median survival was 15 and 25 days, respectively ( $p = 0.026$ , Fig. 2). Likewise, when comparing the survival of deceased patients with and without AKI, median survival values were 15 and 22 days, respectively ( $p = 0.043$ , Fig. 3).

## Discussion

In this case-control study conducted in a second-level hospital in Mexico, in accordance with the literature, we found that AKI is an independent risk factor for mortality in critically ill patients with COVID-19, even after adjustment for age and sex. We also found that patients with AKI died earlier than patients without this complication. It has been reported that patients with COVID-19 who develop AKI have a mortality risk 4.5 times higher compared with those who do not<sup>12</sup>. In our study, the incidence of AKI as an intra-hospital complication was 56%, and the patients who developed it showed a 6.6-fold higher risk of dying. The kidney has been identified as a target



**Figure 2.** Kaplan-Meier survival plots in patients with (dashed line) and without (solid line) obesity and overweight (Ob/Ow). Median survival was 15 and 25 days for the group with and without Ob/Ow, respectively. When comparing both curves a significant  $p = 0.026$  was calculated using the Gehan-Breslow-Wilcoxon test.



**Figure 3.** Kaplan-Meier survival plots in patients with (dashed line) and without (solid line) acute kidney injury (AKI). Median survival was 15 and 22 days for the group with and without AKI, respectively. When comparing both curves a significant  $p = 0.043$  was calculated using the Gehan-Breslow-Wilcoxon test.

organ for virus proliferation in patients with severe SARS-CoV-2 infection<sup>13</sup>, since a direct SARS-CoV-2 invasion into renal parenchyma has been demonstrated, in addition to microthrombosis, acute tubular necrosis, mitochondrial dysfunction, and arterial occlusion<sup>14</sup>. In addition to direct pathophysiological mechanisms, renal dysfunction in the context of COVID-19 may also occur through the systemic

**Table 2. Association of risk factors and mortality in critical COVID-19 patients**

Variable	Value n (%)	COR (95% CI; p)	AOR (95% CI; p)
Acute kidney injury	41 (74.5)	6.2 (2.2-17.6; 0.001)	<b>6.64 (2.14-20.62; 0.001)</b>
Age > 55 years	23 (41.8)	4.4 (1.6-12.3; 0.004)	<b>5.3 (1.57-18.15; 0.007)</b>
Arrhythmia	46 (83.6)	2.9 (1-8.6; 0.048)	<b>5.15 (1.37-19.27; 0.015)</b>
APACHE II score > 25	12 (21.8)	4.9 (1.2-20.1; 0.024)	2.6 (0.47-14.34; 0.271)
Overweight and obesity	37 (67.2)	2.6 (1.15-5.9; 0.021)	2.12 (0.7-6.44; 0.183)
Male sex	34 (61.8)	2.1 (1.2-6.3; 0.013)	0.494 (0.16-1.46; 0.203)
SOFA score > 10	25 (45.4)	1.2 (0.3-1.8; 0.381)	-
NEWS2 score > 10	25 (45.4)	1.31 (0.5-2.9; 0.329)	-
Patient-ventilator asynchrony	17 (30.9)	1.7 (0.6-4.9; 0.177)	-

COR: crude OR (from bivariate regression analysis); AOR: adjusted OR (from multivariable regression analysis). Significant values from multivariable regression are shown in bold.  
Hosmer-Lemeshow test  $p = 0.253$ .

effects of SARS-CoV-2 infection and critical illness<sup>15</sup>. In our study, 74.5% of the deceased patients had AKI, and this was the risk factor with the greatest association with mortality, which is consistent with previously reported data, given that AKI has been pointed out as a marker of severe disease, multiple organ dysfunction, and death from COVID-19<sup>16</sup>.

Importantly, 78% of our population had a least one comorbidity, including obesity/overweight, diabetes mellitus, and hypertension. These comorbidities have been identified as significant risk factors for COVID-19-associated AKI<sup>2</sup>. They are characterized by low-grade inflammation and increased immune senescence, although how these specifically impact the kidney in the setting of COVID-19 is still unknown<sup>15</sup>. Of these comorbidities, obesity has been recognized as one of the most important risk factors for disease severity, use of invasive mechanical ventilation, and death, especially in those under 65 years of age<sup>17</sup>. Several mechanisms have been proposed to explain this relationship, including increased angiotensin-converting enzyme 2 (ACE2) expression. Therefore, a greater presence of ACE2 could be a mechanism that increases the risk of disease and death in COVID-19 patients with obesity<sup>18,19</sup>. In our population, mortality was twice as high in patients with overweight and obesity, which is consistent with the literature<sup>20-22</sup>. However, this association was not significant when the multivariable logistic regression was performed.

Increasing age has also been identified as an independent risk factor associated with mortality in COVID-19 patients, and this is certainly the case with the

Mexican population<sup>23-25</sup>. Furthermore, increasing age has been associated with an increased risk of presenting with symptoms of severity<sup>26</sup>. In our study, age > 55 years was associated with a 5.3-fold risk of mortality, and age tended to be significantly higher in deceased patients compared to survivors.

In contrast to what has been reported in the literature, in our study, 70% of the patients had ventricular extrasystoles. The cardiac manifestations of COVID-19 include arrhythmias, focal or global myocarditis, necrosis, ventricular dysfunction, heart failure, and thrombosis<sup>27-29</sup>. Atrial arrhythmias are the most frequently observed arrhythmias in patients with severe COVID-19. It has been reported that the overall incidence of atrial fibrillation (AF) ranges from 6.6 to 13% in hospitalized COVID-19 patients without a history of atrial arrhythmia<sup>30,31</sup>. Notably, 83% of our deceased patients presented arrhythmias during their ICU stay, whose presence was associated with a 5.15-fold higher risk of dying.

Finally, we would like to highlight that in our study, the length of mechanical ventilation was higher in non-survivors compared to survivors, which is in line with previously published studies<sup>32</sup>.

Limitations of our study include its retrospective nature, as well as potential sampling bias due to convenience sampling, which limits the generalizability of results. In addition, given that this study was conducted in a resource-constrained hospital in Mexico, acute renal replacement therapy strategies (when indicated) were very limited. For instance, slow-continuous renal replacement therapy, the most recommended therapy for hemodynamically unstable critically ill patients, has no

coverage from the state health services, and could therefore not be implemented in our population. Another limitation of our study includes not having the body mass index of the patients due to the impossibility of objectively measuring weight, since hospitalization and ICU beds do not count with digital scales, and therefore, obesity/overweight was ascertained through medical history. Strengths of our study include its sample size, which was adequately powered to detect differences according to the primary outcome. In addition, this study is one of the few to assess the association between AKI and COVID-19 in a Mexican population, along with Casas-Aparicio and colleagues' 2021 study<sup>33</sup>. Esponda-Prado and colleagues also reported on the incidence of AKI among COVID-19 patients, but theirs was a small observational study consisting of solely 22 patients<sup>34</sup>.

## Conclusion

Our findings show that the development of AKI was the main risk factor associated with mortality in critical COVID-19 patients, while other factors such as age > 55 years and cardiac arrhythmias were also associated with this outcome. The kidney is one of the target organs for SARS-CoV-2 proliferation, and other indirect pathophysiological mechanisms may also cause kidney dysfunction; hence, physicians who evaluate COVID-19 patients at hospital admission should integrate the Kidney Disease: Improving Global Outcomes (KDIGO) classification to determine the kidney function and timely identify the presence of acute or chronic kidney damage. This would allow for early management and avoidance of complications where feasible. The management of patients with COVID-19 should categorically include renal function screening and staging on admission to the Emergency Department.

## Funding

The authors declare no funding was received.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical

research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

## References

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard; 2023. Available from: <https://covid19.who.int> [Last accessed on 2023 Apr 25].
2. Zhang J, Pang Q, Zhou T, Meng J, Dong X, Wang Z, et al. Risk factors for acute kidney injury in COVID-19 patients: an updated systematic review and meta-analysis. *Ren Fail.* 2023;45:2170809.
3. Perego AA, Sabiu G, Ottolina D, Colombo R, Casazza G, Gallieni M, et al. Post-mortem renal histopathological findings in 43 COVID-19 patients with acute kidney injury (AKI) deceased in the intensive care unit. *J Nephrol.* 2023;36:605-8.
4. Ronco C, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. *Nat Rev Nephrol.* 2020;16:308-10.
5. Sabaghian T, Kharazmi AB, Ansari A, Omid F, Kazemi SN, Hajikhani B, et al. COVID-19 and acute kidney injury: a systematic review. *Front Med (Lausanne).* 2022;9:705908.
6. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int.* 2020;97:829-38.
7. De Ramos IP, Lazo M, Schnake-Mahl A, Li R, Martinez-Donate AP, Roux AV, et al. COVID-19 outcomes among the hispanic population of 27 large US Cities, 2020–2021. *Am J Public Health.* 2022;112:1034-44.
8. Ricardo AC, Chen J, Toth-Manikowski SM, Meza N, Joo M, Gupta S, et al. Hispanic ethnicity and mortality among critically ill patients with COVID-19. *PLoS One.* 2022;17:e0268022.
9. Magesh S, John D, Li WT, Li Y, Mattingly-App A, Jain S, et al. Disparities in COVID-19 outcomes by race, ethnicity, and socioeconomic status. *JAMA Netw Open.* 2021;4:e2134147.
10. World Health Organization. Therapeutics and COVID-19: Living Guideline; 2023. Available from: <https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-therapeutics-2022.4> [Last accessed on 2023 Apr 25].
11. Ali H, Daoud A, Mohamed MM, Salim SA, Yessayan L, Baharani J, et al. Survival rate in acute kidney injury superimposed COVID-19 patients: a systematic review and meta-analysis. *Ren Fail.* 2020;42:393-7.
12. Puicón-Suárez JB, Zeña-Nañez S, Failloc-Rojas VE. Association between chronic kidney disease and mortality in patients with a confirmed COVID-19 diagnosis. *PeerJ.* 2022;10:e13437.
13. Aukland EA, Klepstad P, Aukland SM, Ghavidel FZ, Buanes EA. Acute kidney injury in patients with COVID-19 in the intensive care unit: Evaluation of risk factors and mortality in a national cohort. *BMJ Open.* 2022;12:e059046.
14. Wishahi M, Kamal NM. Multidisciplinary basic and clinical research of acute kidney injury with COVID-19: pathophysiology, mechanisms, incidence, management and kidney transplantation. *World J Nephrol.* 2022;11:105-14.
15. Nadim MK, Forni LG, Mehta RL, Connor MJ, Liu KD, Ostermann M, et al. COVID-19-associated acute kidney injury: consensus report of the 25<sup>th</sup> Acute Disease Quality Initiative (ADQI) Workgroup. *Nat Rev Nephrol.* 2020;16:747-64.
16. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. *Lancet Respir Med.* 2020;8:738-42.
17. Kompaniyets L, Goodman AB, Belay B, Freedman DS, Suscosky MS, Lange SJ, et al. Body mass index and risk for COVID-19-related hospitalization, intensive care unit admission, invasive mechanical ventilation, and death - United States, March–December 2020. *MMWR Morb Mortal Wkly Rep.* 2021;70:355-61.



18. Al Heialy S, Hachim MY, Hachim IY, Bin Naeem K, Hannawi H, Lakshmanan J, et al. Combination of obesity and co-morbidities leads to unfavorable outcomes in COVID-19 patients. *Saudi J Biol Sci.* 2021;28:1445-50.
19. Emilsson V, Gudmundsson EF, Aspelund T, Jonsson BG, Gudjonsson A, Launer LJ, et al. Serum levels of ACE2 are higher in patients with obesity and diabetes. *Obes Sci Pract.* 2021;7:239-43.
20. Zhou Y, Chi J, Lv W, Wang Y. Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (<scp>Covid</scp>19). *Diabetes Metab Res Rev.* 2021;37:e3377.
21. Pietri L, Giorgi R, Bégu A, Lojou M, Koubi M, Cauchois R, et al. Excess body weight is an independent risk factor for severe forms of COVID-19. *Metabolism.* 2021;117:154703.
22. Vas P, Hopkins D, Feher M, Rubino F, Whyte M. Diabetes, obesity and COVID-19: a complex interplay. *Diabetes Obes Metab.* 2020;22:1892-6.
23. Saldías Peñafiel F, Peñaloza Tapia A, Fariás Nesvadba D, Farcas Oksenberg K, Reyes Sánchez A, Cortés Meza J, et al. Evaluación de los predictores clínicos de infección respiratoria aguda por coronavirus SARS-CoV-2 en población adulta. *Rev Med Chil.* 2021;149:1107-18.
24. Parra-Bracamonte GM, Lopez-Villalobos N, Parra-Bracamonte FE. Clinical characteristics and risk factors for mortality of patients with COVID-19 in a large data set from Mexico. *Ann Epidemiol.* 2020;52:93-8.e2.
25. Salinas-Aguirre JE, Sánchez-García C, Rodríguez-Sánchez R, Rodríguez-Muñoz L, Díaz-Castaño A, Bernal-Gómez R. Características clínicas y comorbilidades asociadas a mortalidad en pacientes con COVID-19 en Coahuila (México). *Rev Clín Esp.* 2022;222:288-92.
26. Mancilla-Galindo J, Kammar-García A, Martínez-Esteban A, Meza-Comparán HD, Mancilla-Ramírez J, Galindo-Sevilla N. COVID-19 patients with increasing age experience differential time to initial medical care and severity of symptoms. *Epidemiol Infect.* 2021;149:e230.
27. Bielecka-Dabrowa A, Cichocka-Radwan A, Lewek J, Pawliczak F, Maciejewski M, Banach M. Cardiac manifestations of COVID-19. *Rev Cardiovasc Med.* 2021;22:365-71.
28. Babapoor-Farrokhran S, Gill D, Walker J, Rasekhi RT, Bozorgnia B, Amanullah A. Myocardial injury and COVID-19: possible mechanisms. *Life Sci.* 2020;253:117723.
29. Maitz T, Parfianowicz D, Wojtek A, Rajeswaran Y, Vyas AV, Gupta R. COVID-19 cardiovascular connection: a review of cardiac manifestations in COVID-19 infection and treatment modalities. *Curr Probl Cardiol.* 2022;48:101186.
30. Lavelle MP, Desai AD, Wan EY. Arrhythmias in the COVID-19 patient. *Hear Rhythm Q2.* 2022;3:8-14.
31. Musikantow DR, Turagam MK, Sartori S, Chu E, Kawamura I, Shivamurthy P, et al. Atrial fibrillation in patients hospitalized with COVID-19. *JACC Clin Electrophysiol.* 2021;7:1120-30.
32. Tanaka C, Tagami T, Nakayama F, Kudo S, Takehara A, Fukuda R, et al. Association between mortality and age among mechanically ventilated COVID-19 patients: a Japanese nationwide COVID-19 database study. *Ann Intensive Care.* 2021;11:171.
33. Casas-Aparicio GA, León-Rodríguez I, Alvarado-de la Barrera C, González-Navarro M, Peralta-Prado AB, Luna-Villalobos Y, et al. Acute kidney injury in patients with severe COVID-19 in Mexico. *PLoS One.* 2021;16:e0246595.
34. Esponda Prado JG, Díaz Greene EJ, Padilla Pérez FJ, Vargas González K, Teniza Frias E, Enríquez Barajas A, et al. Lesión renal aguda en pacientes con COVID-19 en la unidad de terapia intensiva del hospital ángeles pedregal. *Acta Médi Grup Ángel.* 2021;19:229-35.

# Comparison of US elastography and chemical shift magnetic resonance imaging in multifidus muscle fatty degeneration

## *Comparación de la elastografía US y la resonancia magnética con codificación de desplazamiento químico en la degeneración grasa del músculo multifido*

Fatih Kircin<sup>1</sup>, Bahar Yanık<sup>2</sup>, Erdogan Bulbul<sup>2\*</sup>, Emrah Akay<sup>2</sup>, and Gulen Demirpolat<sup>2</sup>

<sup>1</sup>Radiology Clinic, Afyonkarahisar Sandikli State Hospital, Afyonkarahisar; <sup>2</sup>Department of Radiology, Balikesir University School of Medicine, Balikesir, Turkey

### Abstract

**Objective:** The purpose of this study was to investigate the feasibility of the use of shear wave elastography (SWE) in comparison to chemical shift encoding (CSE) magnetic resonance imaging (MRI) for the evaluation of multifidus muscle fatty degeneration in patients with chronic low back pain. **Method:** Multifidus muscles were evaluated with the CSE-MRI and SWE examinations in control and patient groups. With the in-phase and out-phase sequences in CSE-MRI, signal intensity index (SII), and signal intensity suppression ratio (SISR) values; with the SWE method, shear wave velocity values were determined. Differences in the mean values of these parameters per level and study group were analyzed by Student's t-test. **Results:** SWE revealed significantly lower stiffness at the L2-3 level, consistent with the signal index values (SII-SISR) showing increased fatty infiltration on MRI in the patient group. No such relationship was found at the L4-5 level or in control group. **Conclusions:** SWE may be a promising method to show muscle fatty infiltration at L2-3 level in patients with chronic low back pain.

**Keywords:** Fatty infiltration. muscle. Opposed-phase. Shear wave elastography. Stiffness. Low back pain. Magnetic resonance imaging. Multifidus.

### Resumen

**Objetivo:** Investigar la viabilidad del uso de la elastografía de ondas de corte en comparación con la resonancia magnética con codificación de desplazamiento químico (RM-CDQ) para la evaluación de la degeneración grasa del músculo multifido en pacientes con dolor lumbar crónico. **Método:** Los músculos multifidos se evaluaron con RM-CDQ y elastografía de ondas de corte en los grupos de control y de pacientes. Se consideraron las secuencias en fase y fuera de fase en RM-CDQ, y los valores del índice de intensidad de señal y del índice de supresión de intensidad de señal; con el método de elastografía de ondas de corte se determinaron los valores de velocidad de onda de corte. Las diferencias en los valores medios de estos parámetros por nivel y por grupo de estudio se analizaron mediante la prueba t de Student. **Resultados:** La elastografía de ondas de corte reveló una rigidez significativamente menor en el nivel L2-3, consistente con los valores de los índices de señal que muestran una mayor infiltración grasa en la RM en el grupo de pacientes. No se encontró tal relación en el nivel L4-5 ni en el grupo de control. **Conclusiones:** La elastografía de ondas de corte puede ser un método prometedor para mostrar la infiltración grasa muscular a nivel L2-3 en pacientes con dolor lumbar crónico.

**Palabras clave:** Infiltración grasa. Lumbalgia. Resonancia magnética. Músculo multifido. Fase opuesta. Elastografía de ondas de corte. Rigidez.

### \*Correspondence:

Erdogan Bulbul

E-mail: drerdoganbulbul@yahoo.com

Date of reception: 22-01-2024

Date of acceptance: 04-04-2024

DOI: 10.24875/CIRUE.M24000748

Cir Cir (Eng). 2024;92(5):620-627

Contents available at PubMed

www.cirugiaycirujanos.com

2444-0507/© 2024 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

The World Health Organization reports chronic low back pain as one of the leading musculoskeletal problems in the world<sup>1</sup>. Various publications revealed that fatty infiltration of the lumbar multifidus muscle is closely related to low back pain<sup>2-4</sup>. Physical therapy focused on multifidus muscle has been shown to result in regression of fatty infiltration within the muscle, which correlates with functional improvement<sup>5</sup>. Detection of fatty infiltration of lumbar muscles may be highly significant for predicting clinical progression and choosing optimal personalized treatment options<sup>5-8</sup>. Therefore, non-invasive, easily accessible, and reliable imaging techniques are promising tools. Modalities that have been shown useful in the evaluation of intramuscular fatty infiltration include ultrasonography (US), computerized tomography (CT), and magnetic resonance imaging (MRI)<sup>9-13</sup>. Among these different methods, some specific MRI techniques and sequences, such as MR spectroscopy, chemical shift encoded (CSE) imaging stand out<sup>13-15</sup>. CSE MRI is a technique that can show even minimal amounts of fat using different precession frequencies of water and lipid hydrogen protons. Various researchers have shown the feasibility of CSE MR imaging in the evaluation of fatty infiltration of multifidus muscles in individuals with chronic low back pain<sup>16-18</sup>.

Sonoelastography which assesses the stiffness of tissues can be performed by US-integrated techniques such as strain elastography and shear-wave elastography (SWE)<sup>19</sup>. The stiffness of tissues can be evaluated by measuring the velocities of shear waves created in soft tissues with the SWE technique<sup>20</sup>. There are various studies examining multifidus muscle stiffness in patients with low back pain using the SWE method<sup>21-23</sup>. To the best of our knowledge, there is only one study evaluating multifidus muscle stiffness and fatty infiltration of lumbar multifidus muscle in the same case group<sup>24</sup>.

The primary purpose of this study was to assess whether either technique showed a significant difference between patients with chronic low back pain and control subjects. The secondary purpose of this study was to evaluate the feasibility of the SWE technique in the evaluation of multifidus muscle stiffness as a representative of muscle fatty infiltration, using CSE MRI as a non-invasive quantitative method. In addition, it is aimed to reveal whether fatty infiltration of multifidus muscle can be predicted by SWE measurements

by investigating whether there is a correlation between MRI signal index and SWE measurement values in patients with chronic low back pain.

## Methods

### Study population

Adult patients aged 18-60 years, with chronic low back pain for more than 3 months, who were referred to a tertiary academic center for lumbar MRI examination between September 2020 and April 2021 were prospectively enrolled in this study (n = 305).

Individuals with a history of spinal surgery, any congenital orthopedic pathology other than low back pain, trauma, systemic inflammatory disease, advanced osteodegenerative changes (such as central canal stenosis and nerve root compression), spinal infection, neurological or neoplastic disease, and pregnant women were excluded from the study (Fig. 1). The final patient group consisted of 48 patients with chronic low back pain, 27 were female, and 21 were male, aged 22-59 years. A total of 38 normal control subjects 18 women and 20 men, aged 21-59 years, who did not have low back pain were performed lumbar MRI and did not have the features specified in the exclusion criteria in their history were included. Informed consent was obtained from all participating individuals.

### Imaging techniques and image analysis

A 1.5 T MRI scanner (Philips Ingenia, Best, The Netherlands) was used for routine lumbar spinal image acquisition in all participants. In the sagittal plane, T1-weighted images (repetition time [TR]: 430 ms, echo time [TE]: 12 ms, thickness 4 mm, interslice gap 0.4 mm, matrix 240/384r, field of view [FOV] 300 mm, turbo factor [TF] 4, EPI factor 1, and NEX 2) and T2-weighted images (TR: 3000 ms, TE: 120 ms, thickness 4 mm, interslice gap 0.4 mm, matrix 240/384r, FOV 300 mm, TF 17, EPI factor 1, and NEX 2) were obtained. In the axial plane, T2-weighted GRE images (B-FFE) were obtained (TR: 9.6 ms, TE: 4.8 ms, thickness 4 mm, interslice gap 0.4 mm, matrix 148/240r, FOV 160 mm, flip angle (FA) 45°, TF 1, EPI factor 1, and NEX 2). In the control and patient groups who met the criteria, axial images were obtained from the L2-3 and L4-5 levels using an opposed-phase MRI technique, two-point DIXON (mDIXON) sequence

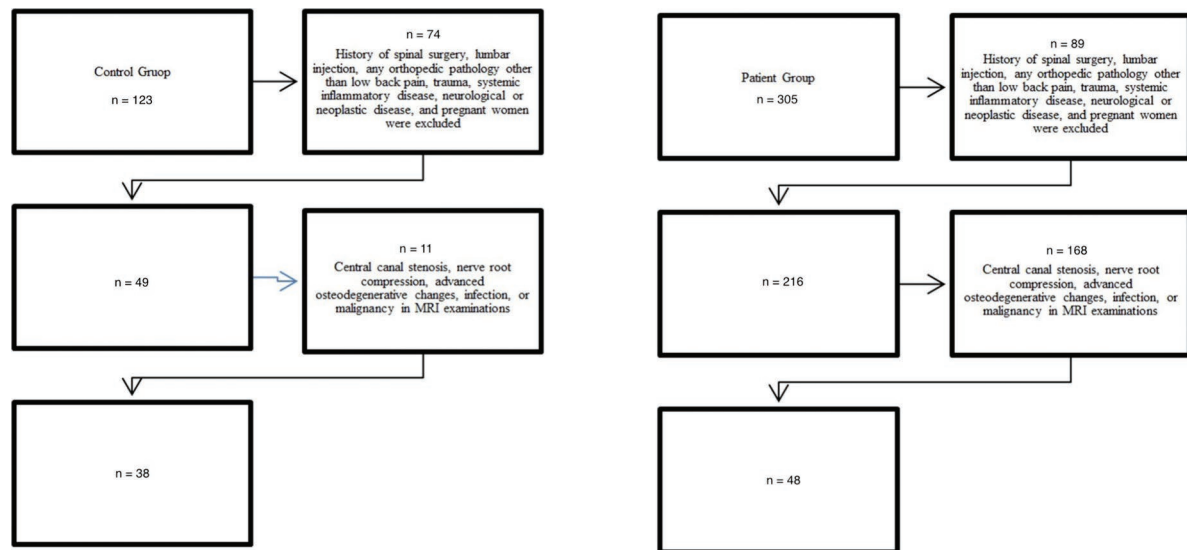


Figure 1. Flow chart as process illustration for case accumulation and exclusion as performed in this work.

(TR:5.8 ms, double TE:4.7 ve 2.4 ms, FA 15°, slice thickness 5 mm, interslice gap-2.5 mm, matrix 189/336r, and FOV 400 mm). In-phase and opposed-phase images were obtained from the same anatomical position, and signal intensity (SI) measurements were made at the workstation at both levels. SI measurements were performed with a circular region of interest (ROI) which was manually placed on the central part of the multifidus muscle. Air in the superficial proximity of skin was chosen as a reference region and measurements with the same sized ROI as in the muscle were obtained. Each measurement was acquired 3 times in a single session by the same 5<sup>th</sup>-year radiology resident. SI index (SII) and SI suppression ratio (SISR) parameters were calculated according to the following formulas using SI values obtained from in and opposed-phase images, as defined in previous articles<sup>17,25</sup>;

- The percentage of change in SI of the multifidus muscle:

$$SII = \frac{[In\text{-}phase\ SI\ multifidus - Opposed\text{-}phase\ SI\ multifidus]}{[in\text{-}phase\ SI]} \times 100$$

- The percentage of change in SI rate of the multifidus muscle compared with air:

$$SISR = \frac{[Opposed\text{-}phase\ (SI\ multifidus/SI\ air)] - In\text{-}phase\ (SI\ multifidus/SI\ air)}{[In\text{-}phase\ (SI\ multifidus/SI\ air)] - 1} \times 100$$

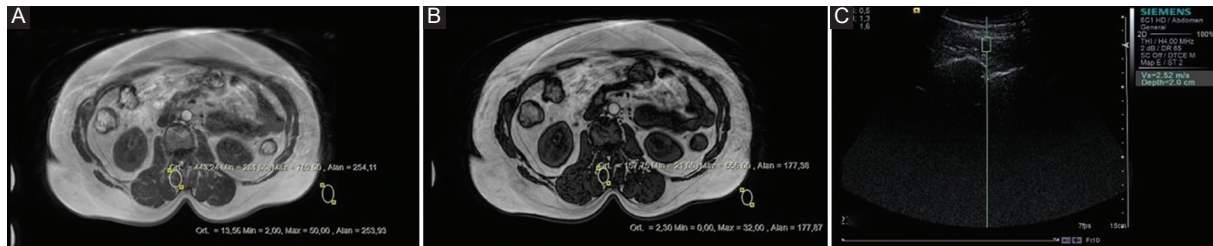
Sonoelastography of lumbar multifidus muscles of participants from control and patient groups was performed by a SWE-capable Acuson S2000 US device (Siemens Healthcare, Erlangen, Germany). A 1-6 Mhz

broadband convex transducer was used to reduce image noise and provide deep tissue penetration. The same operator performed all ultrasound examinations. Participants were placed in the prone position, and a folded towel was placed under their abdomen to reduce lumbar lordosis. Vertebral levels were defined by sonographic determination of the 12<sup>th</sup> rib level. Shear wave velocity (SWV) measurements were made in the sagittal plane, at the same anatomical level and side as MRI measurements; approximately 2 cm right side to the midline and parallel to muscle fibers, with the transducer positioned about 10° medialized, without applying any pressure to the probe. SWV measurements were acquired with a ROI of 0.5 cm × 0.6 cm by placing into multifidus muscle from a maximum depth of 5.5 cm. The minimum and maximum SWV values of seven measurements from each examination area were eliminated, and the arithmetic average of the five values was recorded in m/s.

### Statistical analysis

Statistical analysis of the obtained data was performed using SPSS for Windows, version 22.0 (IBM Corp, NY, USA). Conformity to the normal distribution of SII, SISR, and SWV values of multifidus muscles at L2-3 and L4-5 levels and other variables were evaluated using analytical methods (Kolmogorov–Smirnov/Shapiro-Wilk tests). The correlation relations between the variables measured at both levels were evaluated





**Figure 2.** A 53-year-old female with low back pain. **A:** in-phase and **B:** opposed-phase images. At the L2-3 level, the SII value and the SISR value are 100.31 and 64.55, respectively. **C:** SWV measurement in the multifidus muscle at the same level. The SWV value is 2.52 m/s. SII: signal intensity index; SISR: signal intensity suppression rate; SWV: shear wave velocity; (A-B) Ort: mean signal intensity; Min: minimum signal intensity; Max: maximum signal intensity; Alan: Area; (C) Vs: shear wave velocity.

by Pearson's correlation test for variables with normal distribution. Group differences for SII, SISR, and SWV values of the multifidus muscles at L2-3 and L4-5 levels were compared using Student's t-test. Cases with a type-1 error level below 5% were interpreted as statistically significant. To investigate intrareader agreement, intraclass correlation coefficients (ICCs) were computed.

## Results

The mean age of the control group was 36.16, and the chronic low back pain patient group was 41.79 ( $p = 0.019$ ).

According to the formula, we used in the CSE MRI technique, the semi-quantitative SISR value decreases as the fatty infiltration of the multifidus muscle gradually increases. In the in-phase and out-phase sequences, the fat SI is suppressed, and a higher SII value is obtained according to the formula. In the SWE technique, as the stiffness of tissue decreases, there is a decrease in the SWV value (Figs. 2 and 3). ICCs for SWV, SISR, and SII were 0.73-0.90, 0.80-0.92, and 0.85-0.90, supporting the reproducibility of measurements.

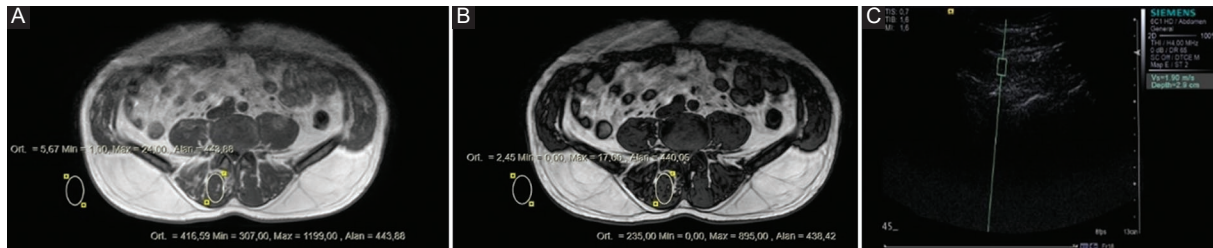
The mean SII and SISR index values obtained from multifidus muscles at L2-3 and L4-5 levels in the control and patient groups by opposed-phase MRI and the mean SWV values measured by SWE from the same levels are given in table 1. There was no statistically significant difference between the control and patient groups regarding SWV, SII, and SISR mean values at L2-3 and L4-5 levels ( $p > 0.05$ ). The correlation between age and multifidus muscle SII, SISR, and SWV values at L2-3 and L4-5 levels in the patient group is shown in table 2. A statistically significant correlation was found between age, and SWV, SII, and SISR values of multifidus muscles at the L2-3

level. As patient age increases, multifidus muscle stiffness decreases, and at MRI, whereas SII increases, SISR decreases, indicating fatty infiltration of the muscle (Fig. 4). At the L4-5 level, no significant correlation between patient age and SWV and SII-SISR index values was noticed.

There was a significant negative correlation between SWV and SII ( $r = -0.317$ ,  $p = 0.028$ ) and a significant positive correlation between SWV and SISR ( $r = 0.336$ ,  $p = 0.019$ ). In other words, as the muscle stiffness decreased, the SII value increased, and the SISR value decreased, indicating fatty infiltration (Fig. 5). No significant correlation was found between SWV and SII ( $r = 0.227$ ,  $p = 0.178$ ) and between SWV and SISR values ( $r = -0.174$ ,  $p = 0.236$ ) for L4-5 level (Table 3).

## Discussion

In our study, no statistically significant multifidus muscle stiffness expressing difference was found between the control group and the patient group with low back pain in terms of SWV mean values at L2-3 and L4-5 levels. This result is different from previous studies with the SWE<sup>21-23</sup>. No significant difference was found between the control and patient groups in terms of SWV and signal index values (SII-SISR). In other words, the lack of statistically significant difference between the control and patient groups in SWV values may be due to the similarity of fatty infiltration levels of multifidus muscles in the control and patient groups. It has previously been reported that the multifidus muscle in patients with low back pain was more rigid than the control group, assessed by the SWE method in the prone position and passive state. It has been suggested that this may be caused by increased tonicity, spasm, and fibrotic changes in the multifidus muscle<sup>21,23,26</sup>. Alis et al. reported a significant decrease in



**Figure 3.** A 50-year-old male with low back pain. **A:** in-phase and **B:** opposed-phase images. At the L4-5 level, the SII value and the SISR value are 43.51 and 30.54, respectively. **C:** SWV measurement in the multifidus muscle at the same level. The SWV value was 1.90 m/s. SII: signal intensity index; SISR: signal intensity suppression rate; SWV: shear wave velocity; (**A-B**) Ort: mean signal intensity; Min: minimum signal intensity; Max: maximum signal intensity; Alan: Area; (**C**) Vs: shear wave velocity.

**Table 1. SWV, SII, and SISR values in the control group and in the patient group**

Levels and measurements	Control group mean (± SD)	Patient group mean (± SD)	p*
L2-3 level multifidus muscle			
SWV	2.81 (± 0.82)	2.68 (± 0.88)	0.474
SII	31.93 (± 11.51)	33.23 (± 13.88)	0.640
SISR	101.68 (± 73.53)	87.98 (± 72.63)	0.391
L4-5 level multifidus muscle			
SWV	2.76 (± 0.71)	2.52 (± 0.57)	0.097
SII	35.19 (± 12.99)	33.38 (± 10.89)	0.493
SISR	118.18 (± 70.9)	94.87 (± 74.41)	0.147

\*Statistically significant  $P < 0.05$ . SD: standard deviation; SWV: shear wave velocity; SII: signal intensity index; SISR: signal intensity suppression ratio.

**Table 2. Correlation results among age and SWV, SII, and SISR values at the L2-3 and L4-5 levels in the patient group**

Parameters	L2-3 multifidus muscle		L4-5 multifidus muscle	
	r*	p**	r*	p**
Age - SWV	-0.305	0.035	-0.228	0.118
Age - SII	0.470	0.001	0.275	0.059
Age - SISR	-0.302	0.037	-0.059	0.692

\* r: Pearson correlation coefficient. \*\*Statistically significant  $p < 0.05$ . SWV: shear wave velocity; SII: signal intensity index; SISR: signal intensity suppression ratio.

**Table 3. Correlation results between SWV and SII values and between SWV and SISR values at the L2-3 and L4-5 levels in the patient group**

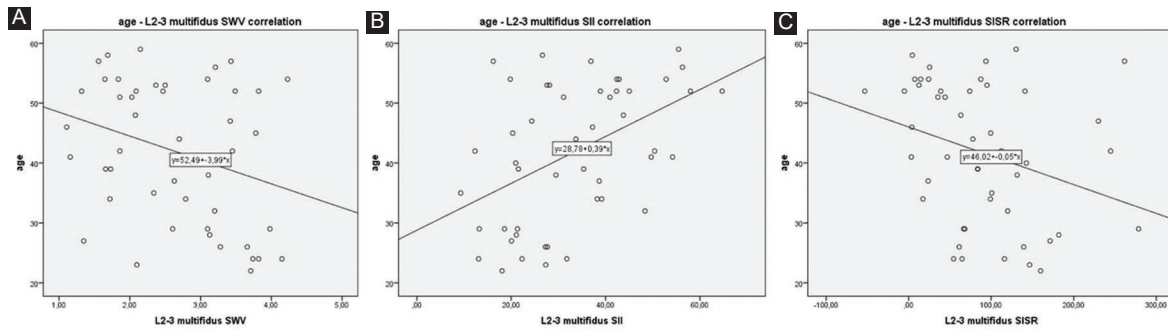
Levels	SWV-SII		SWV-SISR	
	r*	p**	r*	p**
L2-3 level	-0.317	0.028	0.336	0.019
L4-5 level	0.178	0.227	-0.174	0.236

\*r: Pearson correlation coefficient. \*\*statistically significant  $p < 0.05$ . SWV: shear wave velocity; SII: signal intensity index; SISR: signal intensity suppression ratio.

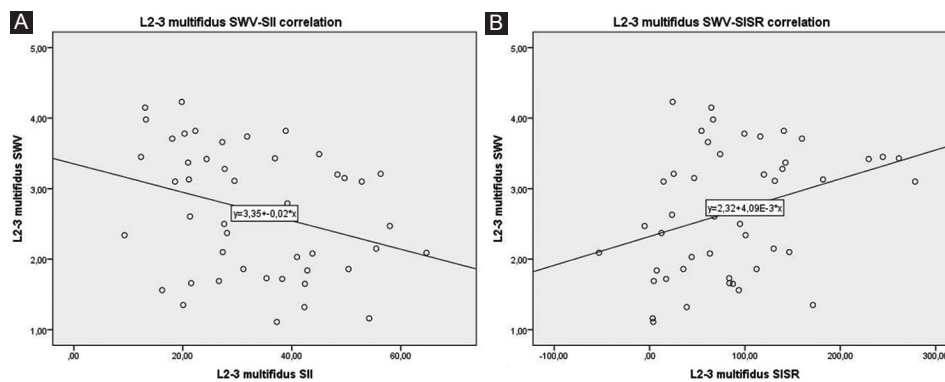
the multifidus muscle stiffness at SWE on the same side and at one lower vertebral level in patients with lumbar disc hernia<sup>22</sup>. They suggested that this result may be due to the fatty infiltration of the multifidus muscle. In another study evaluating the stiffness of the lumbar multifidus muscles in patients with chronic low back pain using the strain elastography method and the degree of fatty infiltration was assessed with the B-mode US images, no statistically significant difference was observed between the patients with chronic low back pain and the control group participants in terms of multifidus muscle stiffness in the passive resting state<sup>24</sup>. It has been stated that these

different study results may be due to the usage of different sonoelastography methods<sup>21,23</sup>. Since the strain elastography technique is reported to be a user-dependent method, and it's difficult to obtain accurate results, it has been indicated that quantitative results can be achieved with the SWE method, which is a less user-dependent technique<sup>21,23</sup>.

It has been previously emphasized in various studies that muscular fatty infiltration may increase depending on age<sup>27-30</sup>. In our study, a decrease in muscle stiffness and an increase in fatty infiltration with increasing age at L2-3 level in the patient group were observed to support this statement. However, no



**Figure 4.** Point distribution graphics of the L2-3 level. **A:** age-SWV, **B:** age-SII, and **C:** age-SISR correlations have been shown. SII: signal intensity index. SISR: signal intensity suppression rate. SWV: shear wave velocity.



**Figure 5.** **A:** SWV-SII. **B:** SWV-SISR point distribution graphics. Correlations of the L2-3 level have been demonstrated. SII: signal intensity index; SISR: signal intensity suppression rate; SWV: shear wave velocity.

statistically significant correlation was found between age and these parameters at the L4-5 level in the patient group. It was thought that this situation might be due to accompanying fibrotic changes in the muscle, as previously reported in the literature<sup>31,32</sup>. Besides, it might have an adverse effect on the ultrasound waves in the thicker thoracolumbar fascia and subcutaneous fat layer in the caudal part at the L4-5 level<sup>33</sup>.

To our knowledge, there is no other study examining the stiffness of multifidus muscles with SWE technique and the muscle fatty infiltration with CSE MRI in the literature. In our study, a correlation was found between SWV values and signals index values indicating that muscle stiffness decreases as fatty infiltration increases in multifidus muscle at the L2-3 level in patients with chronic low back pain. This result is consistent with the knowledge that less rigid sonoelastography values can be detected in muscle tissues with fatty infiltration<sup>31,34</sup>. Our results suggest that SWE may be a promising technique as an alternative

method to MRI in detecting muscle fatty infiltration. However, no correlation was found between SWV measurements and CSE MRI signal index values at the L4-5 level. Similarly no statistical correlation between age and these measurement values. This statistical non-significant correlation at the lower lumbar level may be caused by similar factors. One of these factors may be the complex pathophysiological changes at the lower lumbar levels. It has been reported in various studies that different degenerative pathologies such as disc pathologies, spinal stenosis, and spondylolisthesis may cause more intense degeneration in multifidus muscles at lower lumbar vertebral levels<sup>13,35,36</sup>. However, in this study, these pathologies were exclusion criteria. Besides, it has been stated that fibrotic changes also play a role in multifidus muscle degeneration, as this situation causes an increase in stiffness in muscle fibers and bundles and fibrotic proliferation in the connective tissue. This situation can be seen as increased muscle stiffness in sonoelastographic examination<sup>31,32</sup>. It is thought that

another factor that could cause the lack of a statistical correlation between the measurement values at the lower lumbar level could be the lack of a complete methodological standard for sonoelastography examination<sup>21,23,26,37</sup>. There is a large data pool in the literature consisting of different results obtained from various levels and postures in the sonoelastography examination of posterior paraspinal muscles<sup>21,23,26,37</sup>. It is stated that the image is noisier, especially at the L4-5 level, due to the deeper location of the muscle, and a low-frequency transducer is needed. For this reason, we tried to overcome this problem using a low-frequency convex transducer. Moreover, finally, another factor might be the posterior layer of the thoracolumbar fascia which is thicker in the caudal part at the L4-5 level and strongly attenuates ultrasound waves<sup>33</sup>.

Our study has some limitations. First, there were the limited number of patients in our control and study groups. Second, since there is no consensus about how to perform the SWE examination of multifidus muscles, our study was based on some application examples in the literature<sup>21,23,26</sup>. Third, our study did not include the participants' body mass index (BMI) values. However, there are studies in the literature reporting no relationship between the fatty infiltration of multifidus muscle and BMI<sup>38,39</sup>. Finally, our study is not supported by the fat fraction measurement, MR spectroscopy data, or histopathological data, which is the gold standard for demonstrating fibrosis and fatty infiltration.

## Conclusions

In this study, a statistically significant correlation was found between SWE-assessed muscle stiffness and MRI-assessed fatty infiltration in multifidus muscles at the L2-3 level in the chronic low back pain group but not at the L4-5 level or in control group.

These results suggest that the SWE technique, which is a more practical, easily accessible, and inexpensive method, maybe a promising radiological examination in the detection of multifidus muscle fatty infiltration in symptomatic patients for upper leaves of lumbar paravertebral muscles.

## Acknowledgments

The authors would like to thank the ethics committee for the approval of this work.

## Compliance with ethical standards

Ethical approval: Informed consent for the study was obtained from all human subjects. The study was approved by the Clinical Research Ethics Committee of our faculty (No. 73023407/604.01.01/37892) and all procedures followed were in accordance with the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research involving Human Subjects, 2013.

## Funding

The authors declare that they have not received funding.

## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained approval from the ethics committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

## References

1. Kaplan W, Wirtz V, Mantel A, Béatrice PS. Priority medicines for Europe and the world update 2013 report. *Methodology*. 2013;2:99-102.
2. Parkkola R, Rytökoski U, Kormano M. Magnetic resonance imaging of the discs and trunk muscles in patients with chronic low back pain and healthy control subjects. *Spine (Phila Pa 1976)*. 1993;18:830-6.
3. Kjaer P, Bendix T, Sorensen JS, Korsholm L, Leboeuf-Yde C. Are MRI-defined fat infiltrations in the multifidus muscles associated with low back pain? *BMC Med*. 2007;5:1-10.
4. Sollmann N, Bonenheim NB, Joseph GB, Chachad R, Zhou J, Akkaya Z, et al. Paraspinal muscle in chronic low back pain: comparison between standard parameters and chemical shift encoding-based water-fat MRI. *J Magn Reson Imaging*. 2022;56:1600-8.
5. Woodham M, Woodham A, Skeate JG, Freeman M. Long-term lumbar multifidus muscle atrophy changes documented with magnetic resonance imaging: a case series. *J Radiol Case Rep*. 2014;8:27.



6. Hebert JJ, Le Cara EC, Koppenhaver SL, Hoffman MD, Marcus RL, Dempsey AR, et al. Predictors of clinical success with stabilization exercise are associated with lower levels of lumbar multifidus intramuscular adipose tissue in patients with low back pain. *Disabil Rehabil.* 2020;42:679-84.
7. Osorio W, Ceballos C, Moyano J. Effectiveness of acute post-operative pain management by the acute pain service. *Cir Cir.* 2022;90:197-201.
8. Jermy JE, Copley PC, Poon MT, Demetriades AK. Does pre-operative multifidus morphology on MRI predict clinical outcomes in adults following surgical treatment for degenerative lumbar spine disease? A systematic review. *Eur Spine J.* 2020;29:1318-27.
9. Flicker PL, Fleckenstein JL, Ferry K, Payne J, Ward C, Mayer T, et al. Lumbar muscle usage in chronic low back pain. Magnetic resonance image evaluation. *Spine (Phila Pa 1976).* 1993;18:582-6.
10. Hides JA, Stokes MJ, Saide M, Jull GA, Cooper DH. Evidence of lumbar multifidus muscle wasting ipsilateral to symptoms in patients with acute/subacute low back pain. *Spine (Phila Pa 1976).* 1994;19:165-72.
11. Keller A, Brox JI, Gunderson R, Holm I, Friis A, Reikeras O. Trunk muscle strength, cross-sectional area, and density in patients with chronic lowback pain randomized to lumbar fusion or cognitive intervention and exercises. *Spine (Phila Pa 1976).* 2004;29:3-8.
12. Hicks GE, Simonsick EM, Harris TB, Newman AB, Weiner DK, Nevitt MA, et al. Cross-sectional associations between trunk muscle composition, back pain, and physical function in the health, aging, and body composition study. *J Gerontol A Biol Sci Med Sci.* 2005;60:882-7.
13. Kalichman L, Carmeli E, Been E. The association between imaging parameters of the paraspinal muscles, spinal degeneration, and low back pain. *Biomed Res Int.* 2017;2017:2562957.
14. Takashima H, Takebayashi T, Ogon I, Yoshimoto M, Morita T, Umamura R, et al. Analysis of intra and extramyocellular lipids in the multifidus muscle in patients with chronic low back pain using MR spectroscopy. *Br J Radiol.* 2018;91:20170536.
15. Han G, Jiang Y, Zhang B, Gong C, Li W. Imaging evaluation of fat infiltration in paraspinal muscles on MRI: a systematic review with a focus on methodology. *Orthop Surg.* 2021;13:1141-8.
16. Paalanne N, Niinimäki J, Karppinen J, Taimela S, Mutanen P, Takatalo J, et al. Assessment of association between low back pain and paraspinal muscle atrophy using opposed-phase magnetic resonance imaging: a population-based study among young adults. *Spine (Phila Pa 1976).* 2011;36:1961-8.
17. Yanik B, Keyik B, Conkbayir I. Fatty degeneration of multifidus muscle in patients with chronic low back pain and in asymptomatic volunteers: quantification with chemical shift magnetic resonance imaging. *Skeletal Radiol.* 2013;42:771-8.
18. Schlaeger S, Inhuber S, Rohrmeier A, Deickmeyer M, Freitag F, Klupp E, et al. Association of paraspinal muscle water-fat MRI-based measurements with isometric strength measurements. *Eur Radiol.* 2019;29:599-608.
19. Lee SK, Jung JY, Kang YR, Jung JH, Yang JJ. Fat quantification of multifidus muscle using T2-weighted Dixon: which measurement methods are best suited for revealing the relationship between fat infiltration and herniated nucleus pulposus. *Skeletal Radiol.* 2020;49:263-71.
20. Hug F, Hodges PW, Tucker K. Muscle force cannot be directly inferred from muscle activation: illustrated by the proposed imbalance of force between the vastus medialis and vastus lateralis in people with patellofemoral pain. *J Orthop Sports Phys Ther.* 2015;45:360-5.
21. Masaki M, Aoyama T, Murakami T, Yanase K, Ji X, Tatehuchi H, et al. Association of low back pain with muscle stiffness and muscle mass of the lumbar back muscles, and sagittal spinal alignment in young and middle-aged medical workers. *Clin Biomech (Bristol, Avon).* 2017;49:128-33.
22. Alis D, Durmaz ES, Alis C, Erol BC, Okur B, Kizilkilic O, et al. Shear wave elastography of the lumbar multifidus muscle in patients with unilateral lumbar disk herniation. *J Ultrasound Med.* 2019;38:1695-703.
23. Murillo C, Falla D, Rushton A, Sanderson A, Heneghan NR. Shear wave elastography investigation of multifidus stiffness in individuals with low back pain. *J Electromyogr Kinesiol.* 2019;47:19-24.
24. Chan ST, Fung PK, Ng NY, Ngan TL, Chong MY, Tang CN, et al. Dynamic changes of elasticity, cross-sectional area, and fat infiltration of multifidus at different postures in men with chronic low back pain. *Spine J.* 2012;22:381-8.
25. Gokalp G, Yildirim N, Yazici Z, Ercan I. Using chemical-shift MR imaging to quantify fatty degeneration within supraspinatus muscle due to supraspinatus tendon injuries. *Skeletal Radiol.* 2010;39:1211-7.
26. Koppenhaver S, Gaffney E, Oates A, Eberle L, Young B, Hebert J, et al. Lumbar muscle stiffness is different in individuals with low back pain than asymptomatic controls and is associated with pain and disability, but not common physical examination findings. *Musculoskelet Sci Pract.* 2020;45:102078.
27. Hadar H, Gadoth N, Heifetz M. Fatty replacement of lower paraspinal muscles: normal and neuromuscular disorders. *AJR Am J Roentgenol.* 1983;141:895-8.
28. Hebert JJ, Kjaer P, Fritz JM, Walker BF. The relationship of lumbar multifidus muscle morphology to previous, current, and future low back pain: a 9-year population-based prospective cohort study. *Spine (Phila Pa 1976).* 2014;39:1417-25.
29. Lee SH, Park SW, Kim YB, Nam TK, Lee YS. The fatty degeneration of lumbar paraspinal muscles on computed tomography scan according to age and disc level. *Spine J.* 2017;17:81-7.
30. Mackintosh S, Young A, Muirhead J, Lee A, Sim JH. A pilot study: can shear wave elastography predict fatty infiltration of the supraspinatus muscle? *Sonography.* 2020;7:97-109.
31. Brown SH, Gregory DE, Carr JA, Ward SR, Masuda K, Lieber RL. ISS-LS prize winner: adaptations to the multifidus muscle in response to experimentally induced intervertebral disc degeneration. *Spine.* 2011;36:1728-36.
32. Brown E, Yoshitake Y, Shinohara M, Ueda J. Automatic analysis of ultrasound shear-wave elastography in skeletal muscle without non-contrastile tissue contamination. *Int J Intell Robot Appl.* 2018;2:209-25.
33. Moreau B, Vergari C, Gad H, Sandoz B, Skalli W, Laporte S. Non-invasive assessment of human multifidus muscle stiffness using ultrasound shear wave elastography: a feasibility study. *Proc Inst Mech Eng H.* 2016;230:809-14.
34. Koppenhaver SL, Scutella D, Sorrell BA, Yahalom J, Fernandez-de-Las-Peñas C, Childs JD, et al. Normative parameters and anthropometric variability of lumbar muscle stiffness using ultrasound shear-wave elastography. *Clin Biomech (Bristol, Avon).* 2019;62:113-20.
35. Albert HB, Briggs AM, Kent P, Byrthagen A, Hansen C, Kjaergaard K. The prevalence of MRI-defined spinal pathoanatomies and their association with modic changes in individuals seeking care for low back pain. *Eur Spine J.* 2011;20:1355-62.
36. Hodges PW, Danneels L. Changes in structure and function of the back muscles in low back pain: different time points, observations, and mechanisms. *J Orthop Sports Phys Ther.* 2019;49:464-76.
37. Ma CZ, Ren LJ, Cheng CL, Zheng YP. Mapping of back muscle stiffness along spine during standing and lying in young adults: a pilot study on spinal stiffness quantification with ultrasound imaging. *Sensors.* 2020;20:7317.
38. Mengiardi B, Schmid MR, Boos N, Pfirrmann CWA, Brunner F, Elfering A, et al. Fat content of lumbar paraspinal muscles in patients with chronic low back pain and in asymptomatic volunteers: quantification with MR spectroscopy. *Radiology.* 2006;240:786-92.
39. Shapiro L, Harish M, Hargreaves B, Staroswiecki E, Gold G. Advances in musculoskeletal MRI: technical considerations. *J Magn Reson Imaging.* 2012;36:775-87.

# Morphology of ulnar trochlear notch and defining ideal position for olecranon osteotomy

## Morfología de la ulna muesca troclear y definición de la posición ideal para la osteotomía del olecranon

Milan Milinkov<sup>1\*</sup>, Nikola Vučinić<sup>2</sup>, Mirko Obradović<sup>3</sup>, Nikola Vukosav<sup>3</sup>, Milan Tošić<sup>3</sup>, and Bojana Krstonošić<sup>2</sup>

<sup>1</sup>Faculty of Medicine, University of Novi Sad; <sup>2</sup>Department of Anatomy, Faculty of Medicine, University of Novi Sad; <sup>3</sup>Clinic for Orthopedic Surgery and Traumatology, Clinical Center of Vojvodina. Novi Sad, Serbia

### Abstract

**Objective:** The aim of the study was to calculate the most important parameters of ulna and to determine its gender. Classifying trochlear notch joint surface types and to establish their representation in Serbian population. To determine the ideal position for olecranon osteotomy. **Material and methods:** The study included 69 bones. Gender determination was performed using digital scale and photographs of the ulna. The bones weight, maximum and physiological length were measured. The place for the ideal position of olecranon osteotomy (projection of the bare area on its posterior wall) was determined on profile images. **Results:** Gender related, 45 (65.21%) bones belonged to males, 24 (34.79%) ulnas belonged to females. Type I of the bare area was present in 38 (55%) ulnas, type II in 20 (29%), whereas type III was present in 11 (16%) bones. The average value for the ideal position of olecranon osteotomy was 23.02 mm. In males' ulnas, it was 23.22 mm, in females, it was 22.59 mm. **Conclusion:** Type I of the bare area is the most common type of trochlear notch joint surface in Serbian population. The average value for the ideal position of olecranon osteotomy was 23.02 mm. We believe that a uniform name for the bare area should be established.

**Keywords:** Ulna. Olecranon process. Trochlear notch. Osteotomy. Gender.

### Resumen

**Objetivos:** Calcular los parámetros más importantes del cúbito y determinar su género. Clasificar los tipos de superficie de la articulación de la escotadura troclear y establecer su representación en la población serbia. Determinación de la posición ideal para la osteotomía del olécranon. **Material y métodos:** El estudio incluyó 69 huesos. La determinación del sexo se realizó mediante escala digital y fotografías del cúbito. Se midió el peso de los huesos, la longitud máxima y fisiológica. El lugar para la posición ideal de la osteotomía del olécranon se determinó en imágenes de perfil. **Resultados:** Relacionado con el género, 45 (65.21%) huesos pertenecían a hombres, 24 (34.79%) cúbitos pertenecían a mujeres. El tipo I del área descubierta estuvo presente en 38 (55%) ulna, el tipo II en 20 (29%), mientras que el tipo III estuvo presente en 11 (16%) huesos. El valor medio para la posición ideal de la osteotomía del olécranon fue de 23,02 mm. **Conclusión:** El área desnuda tipo I es el tipo más frecuente de superficie articular de muesca troclear en la población serbia. El valor promedio para la posición ideal de la osteotomía del olécranon fue de 23,02 mm. Creemos que se debe establecer un nombre uniforme para el área descubierta.

**Palabras clave:** Ulna. Proceso del olécranon. Escotadura troclear. Osteotomía. Género.

#### \*Correspondence:

Milan Milinkov

E-mail: 014293@mf.uns.ac.rs

Date of reception: 22-10-2022

Date of acceptance: 21-03-2023

DOI: 10.24875/CIRUE.M23000749

Cir Cir (Eng). 2024;92(5):628-633

Contents available at PubMed

www.cirugiaycirujanos.com

2444-0507/© 2023 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Ulna is one of the bones of the forearm and it is positioned on the medial side of the radius and slightly behind it, in physiological position of supination. According to its shape, ulna belongs to long bones (*ossa longa*) and it is also an even bone. We distinguish the body and two end parts of the bone<sup>1</sup>. There are a trochlear notch, olecranon, and coronoid process on proximal end of ulna. Trochlear notch (*incisura trochlearis*) represents a concave joint surface and it is positioned between coronoid process and olecranon. Bare area divides it into two slopes corresponding to the joint surfaces which articulate with the trochlea of humerus. Olecranon is located at the upper back of the proximal part of the ulna. It tends to have a cube shape, on the front side being recessed into a smooth surface which forms part of the trochlear notch. The triceps attaches to the upper side of the olecranon and its posterior surface is rough and subcutaneous. Coronoid process represents front bottom eminence of the proximal part of ulna. Its shape resembles a four-sided pyramid. Upper side of coronoid process makes the bottom wall of the trochlear notch. On the lateral side, there is a radial notch (*incisura radialis*) which represents joint surface as well<sup>1</sup>.

Data about gender affiliation are very important in every anthropological research, although it is not a simple task to determine gender on a single bone<sup>2,3</sup>. There are several ways of determining gender affiliation of ulna in the literature. We assume that authors Reddy and Doshi described optimal parameters<sup>3</sup>.

Several classifications of trochlear notch are described regarding shapes of its joint surfaces. They indicate generally present anatomical variation, with certain degree of representation in different populations<sup>4,5</sup>.

As fractures of distal humerus are relatively common injuries of the upper extremity, from the clinical point, type of trochlear notch joint surface is significant for performing olecranon osteotomy during operative treatment of the mentioned fractures. Olecranon osteotomy with opened reposition and internal fixation represents widely accepted method of operative treatment for type C fractures of distal humerus (complete intraarticular fracture)<sup>5</sup>. Compared to other surgical approaches to distal humerus, it provides the best approach<sup>6</sup>, thus increasing the success of the surgical treatment. Furthermore, the authors suggest the possible impact of variations in trochlear notch joint surfaces on arthroscopic elbow surgeries, design



**Figure 1.** Intraoperative view of the chevron olecranon osteotomy (Photo from the personal archive of intraoperative photos of co-author Dr. Mirko Obradović).

of prostheses for performing elbow arthroplasty, as well as its impact on elbow radiological imaging<sup>5</sup>. Projection of the bare area on posterior wall of ulna represents, “entry point” for performing olecranon osteotomy itself<sup>5,7</sup> as it is well known that the potential joint surface cartilage damage would lead to arthrosis of the affected joint. Besides, current recommendation from AO Foundation for olecranon osteotomy is to perform the chevron osteotomy<sup>8</sup> (Fig. 1). Bare area projection on the back side of the ulna is of crucial importance for such a procedure. Clinical importance of bare area is not supported in current anatomical terminology<sup>9</sup>. In other words, there is no specific name for transverse ridge (bare area) although it significantly morphologically differs from the rest of the trochlear notch<sup>10</sup>.

We presume that examining different parameters on ulna, as well as types of trochlear notch joint surfaces regarding their shape will bring important data related to Serbian population. We also believe that the indicative recognition of the bare area projection on the ulnar back wall would contribute to significantly better results in surgical treatment, intraoperatively, as well

as postoperatively, resulting in easier recovery and better function of the elbow. Goals of our paper were first to calculate the most important parameters of ulna and to determine its gender, based on the results. Second, the goal was to classify trochlear notch joint surface types and to establish their representation in Serbian population. Third, it was to determine the ideal position for olecranon osteotomy.

## Materials and methods

The research was conducted at the Department of Anatomy, Faculty of Medicine, University of Novi Sad. It included 69 bones from the Osteological museum which were of an unknown age. The research exclusion criteria were bone damages and previous fractures. All bones were photographed by *Canon EOS2000D* camera, using a photo stand. During the process, they were on the same distance and under the same angle compared to the camera. Further, photo processing and parameters calculation were done using *ImageJ 1.53K* software. The same person performed both photographing and photo processing.

We classified types of trochlear notch joint surfaces into three types, through direct visualization by the two people, based on the research of Totlis et al.<sup>5</sup>.

- Type I – Completely divided olecranon and coronoid process joint surfaces.
- Type II – Connected olecranon and coronoid process joint surfaces with constriction.
- Type III – Connected olecranon and coronoid process joint surfaces without constriction<sup>5</sup> (Fig. 2).

The following parameters were measured to define ulna's gender affiliation, using a digital scale and photographs of ulnas:

- Ulna's weight
- Maximal length – The distance between the highest point of olecranon and the lowest point of ulna's styloid process<sup>3</sup>.
- Physiological length – the distance between the most distal points on the coronoid process surface and on the lower surface of ulna distal end part (excluding styloid process)<sup>3</sup>.

Location of the ideal position for olecranon osteotomy was defined on bones' profile pictures, by measuring the distance from insertion of triceps on the top of the olecranon to the projection of bare area on the posterior wall of ulna (Fig. 3)<sup>8</sup>. Bones with type III bare area were excluded from the sample (when determining the ideal olecranon osteotomy position). Due to connected joint

surfaces, it is not possible to avoid damaging cartilage while performing this procedure. Thus, it is impossible to determine the ideal position for the procedure itself.

The program used for data processing was Statistical Package for the Social Sciences which works under the Microsoft Windows environment. The results are presented using graphs and tables. The descriptive statistics is shown (frequencies and percentages for categorical data, as well as arithmetic means and standard deviations for quantitative data). Since the results of the osteotomy position parameters are expressed quantitatively, it is established that presumption about normal result distribution ( $p > 0.05$ ) was fulfilled using the Shapiro–Wilk test. T-test was used for independent samples to examine differences between male and female ulnas, along with both left and right side of the body in terms of the ideal osteotomy position.  $\chi^2$  test was used for categorical data to determine the correlation between male and female ulnas, the side of the body where the bone is located on one side and the frequency of three basic types of trochlear notch joint surfaces on the other side.

The research was approved by the Medical faculty Ethics commission, in Novi Sad (date: 08 December 2021; decision number: 01-39/119/1).

## Results

According to the bone gender, 45 (65.21%) were males, while 24 (34.79%) were females. The sample contained 37 (52.62%) right and 32 (46.38%) left bones. Descriptive statistical indicators of the measured parameters are shown in table 1.

Type I bare area was represented by 38 ulnas, type II by 20, whereas type III was represented by 11 bones, out of the total number of ulnas in the sample (Fig. 4).

Numerical representation of trochlear notch joint surfaces regarding gender is shown in figure 5. Type I bare area was present in 62% of male ulnas, and 42% at females, type II was noted in 27% of male and 33% of female ulnas, while type III was noticed in 11% of male and 25% of female bones. Statistically relevant connection was not established between male and female ulnas and the presence of three basic trochlear notch joint surface types.  $\chi^2$  (2, N = 69) = 3.335,  $p = 0.189$ .

Joint surfaces frequency distribution in the sample showed that 19 ulnas had type I bare area in both left and right bones, type II was noted seven times in left,



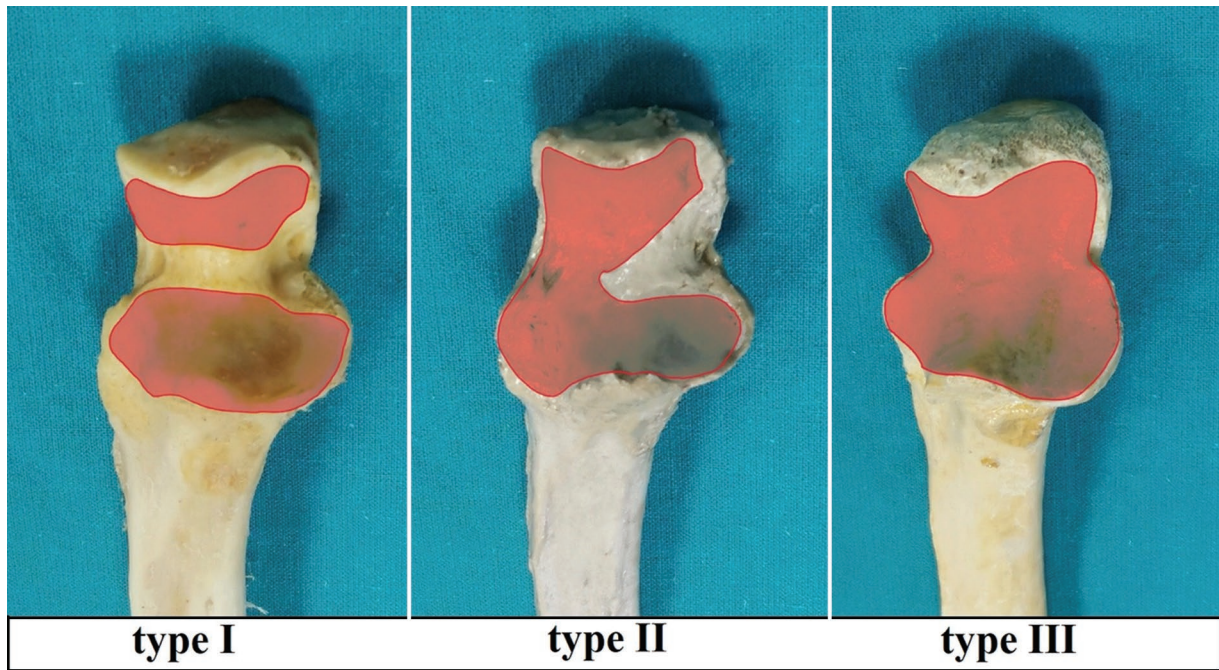


Figure 2. Representation of basic types of trochlear notch joint surfaces.

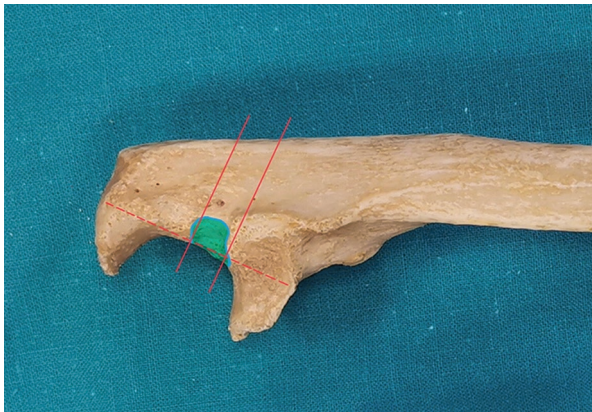


Figure 3. Representation of the bare area projection on the posterior wall of ulna as an entry point for performing the chevron olecranon osteotomy.

and 13 times in the sample of right bones, whereas type III was identified six times in left and five times in right bones. Statistically relevant association between left and right side of the body and frequency of three basic types of trochlear notch joint surfaces were not determined.  $\chi^2$  (2, N = 69) = 1.537,  $p = 0.464$ .

The average value for the ideal position of olecranon osteotomy in the sample (58 bones) was 23.02 mm. In males' ulnas, it was 23.22 mm, while in females, it was 22.59 mm. The results of the t-test indicated that no statistically significant differences were found between

male and female ulnas regarding the ideal average position for performing osteotomy ( $t$  [56] = 0.619,  $p = 0.538$ ).

Related to bare area, average value for the ideal position of olecranon osteotomy in type I was 23.31 mm, while in type II it was 22.47 mm. In right ulnas ideal position for performing olecranon osteotomy was 22.61 mm, while in the left bones it was 23.52 mm. The results of the t-test indicated that no statistically significant differences were found between the left and right side of the body in terms of the ideal average position for performing osteotomy ( $t$  [56] = 0.976,  $p = 0.333$ ).

## Discussion

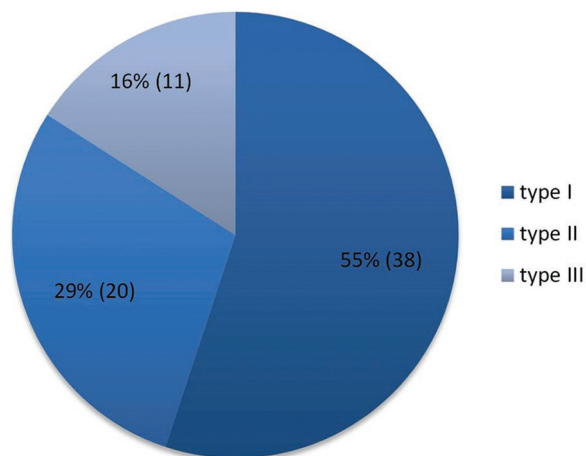
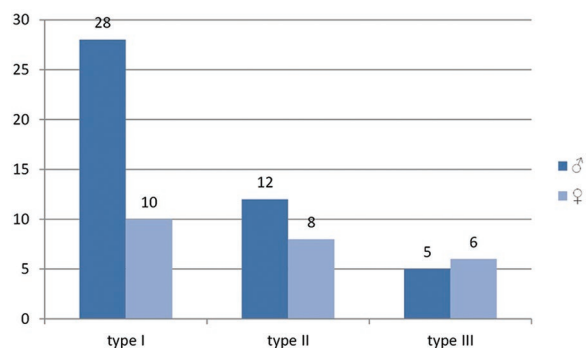
Determination of cadaver sex based on skeletal remains certainly belongs to anthropological sciences. Besides gaining anthropological knowledge, it also provides us with significant forensic data<sup>2</sup>.

In literature, there are several trochlear notch classifications regarding shapes of its joint surfaces<sup>4,5</sup>. Even though classification on three basic types is described in several research papers<sup>5,11</sup>, it is notable that, in anatomical and orthopedics textbooks completely divided, joint surface (type I) is the only one listed<sup>12-14</sup>. We did not find a significant number of scientific papers which included the representation of types of ulnar trochlear notch joint surfaces. Representation of mentioned

**Table 1. Representation of descriptive statistical indicators**

Parameters	n	Min	Max	M	SD
Weight (g)	69	19	74	47.25	13.53
Maximal length (mm)	69	227.73	304.03	261.87	18.35
Physiological length (mm)	69	195.20	271.38	227.85	16.87
Osteotomy position (mm)	58	14.73	31.18	23.03	3.53

N: number of respondents; Min: minimum; Max: maximum; M: arithmetic mean; SD: standard deviation.

**Figure 4.** Representation of trochlear notch joint surface types in our sample.**Figure 5.** Representation of trochlear notch joint surfaces types according to gender.

structure in Serbian population correlates with the results of other European authors<sup>5</sup>. Both in ours and in mentioned research, types I and II are stated as the predominant, with representation of more than 80%. We believe that knowing the projection of the bare area on posterior wall of the ulna is of crucial importance when performing

olecranon osteotomy, since it is possible to avoid cartilage damage in mentioned trochlear notch types.

In our study, we decided to use bone weight, maximal length of ulna, and physiological length of ulna when determining bone gender. Other researchers showed that two of three mentioned parameters (bone weight and physiological length of bone) are the most discriminatory variables for determining the cadaver gender related to the ulna, with overall accuracy of 93.2%<sup>3</sup>. Due to the significant differences in male's and female's musculoskeletal system, we feel that determination of bones gender is very useful in our study. Type II bare area is relatively equally represented in males and females in Serbian population. Type I was more common in males, while type III was more frequent in female's ulnas. We attribute different bone representation to non-identical biological development of men and women. This result should be taken with certain amount of constraint due to unequal number of bones of both genders.

Types of trochlear notch articular surfaces have a big role in orthopedics surgery. Some authors state different positions as entry point for performing olecranon osteotomy – at the level of the trochlea of humerus<sup>15,16</sup>, then through the trochlear notch itself<sup>17</sup>, as well as 3–4 cm from the top of the olecranon<sup>18</sup>. Newer researches cite the projection of bare area on the posterior wall of ulnas entry point for performing olecranon osteotomy<sup>5,8,10</sup> as a part of operative treatment of fractures of the distal end of the humerus. Based on recent research, we determined the ideal position for olecranon osteotomy based on the projection of the bare area on the posterior wall of the ulna. Compared to our results, Chinese authors report a slightly lower value of the ideal position for performing olecranon osteotomy, which is 22 mm<sup>8</sup>, and we assume that the difference of approximately 1 mm is insignificant. It is our opinion that determining the average position for olecranon osteotomy brings significant data to orthopedists to avoid damage of the articular surfaces, which would certainly lead to certain postoperative complications.

We often come across authors' hypotheses that different anatomical characteristics can be found among the same bones, on opposite sides of the body (right and left bones)<sup>19</sup>. Yet, there is a relative uniformity of the types of articular surfaces of the trochlear notch between the left and right ulnas in our sample. Six more right bones with the type II trochlear notch are due to the fact that there were more right ulnas in the entire sample. In literature, authors use different names to describe the part of the articular surface

without cartilage, that is, the bare area itself. However, its name does not exist in the official anatomical literature<sup>9</sup>. Based on the anatomical structure of the liver, the *area nuda*, we feel that a uniform name for the bare area should be established. Considering its anatomical appearance and histological structure<sup>14</sup>, we suggest the name *area ossea*. The new, specific name would greatly contribute to a better understanding and easier identification of the described structure.

## Conclusions

Type I bare area is the most common type of articular surface in Serbian population. The average value for the ideal position of olecranon osteotomy in the sample was 23.02 mm, and no statistically significant differences were found between male and female ulnas regarding the ideal average position for performing osteotomy. Furthermore, no statistically significant differences were found between the left and right side of the body in terms of the ideal average position for performing osteotomy. We believe that knowing the projection of the bare area on posterior wall of the ulna is of crucial importance when performing olecranon osteotomy, since it is possible to avoid cartilage damage in different trochlear notch types. The new special name *area ossea*, which we suggest for the examined structure, would greatly contribute to a better understanding and easier identification.

## Funding

The authors declare no funding was received.

## Conflicts of interest

All authors declare that they have no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical

research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data, and informed consent was not required for this retrospective observational study.

## References

1. Franco-Valencia M, Torres-González R, Fuentes-Figueroa S. Radiographic measurements of the wrist in healthy Mexicans. *Cir Cir*. 2006; 74:335-42.
2. Purkait R. Measurements of ulna--a new method for determination of sex. *J Forensic Sci*. 2001;46:924-7.
3. Reddy BB, Doshi MA. Sex determination from adult human ulna by stepwise discriminant function analysis. *Int J Res Med Sci*. 2017; 6:5128-31.
4. Yamaguchi B. The bipartient tendency of the articular surface of the trochlear notch in the human ulna. *Okajimas Folia Anat Jpn*. 1972; 49:23-35.
5. Totlis T, Otountzidis N, Papadopoulos S, Piagkou M, Natsis K. Ulnar trochlear notch articular surface has three morphological patterns: a neglected major anatomical feature. *Surg Radiol Anat*. 2019;41:1333-6.
6. Luegmair M, Timofiev E, Chirpaz-Cerbat JM. Surgical treatment of AO Type C distal humeral fractures: internal fixation with a Y-shaped reconstruction (Lambda) plate. *J Shoulder Elbow Surg*. 2008;17:113-20.
7. Wilkinson JM, Stanley D. Posterior surgical approaches to the elbow: a comparative anatomic study. *J Shoulder Elbow Surg*. 2001;10:380-2.
8. Ao R, Zhang X, Li D, Chen F, Zhou J, Yu B. The bare area of the proximal ulna: an anatomic study with relevance to chevron osteotomy. *J Hand Surg Am*. 2017;42:471.e1-471.e6.
9. FIPAT. Terminologia Anatomica. 2<sup>nd</sup> ed. FIPAT.Library.Dal.Ca. Federative International Programme for Anatomical Terminology; 2019.
10. Wang A, Mara M, Hutchinson DT. The proximal ulna: an anatomic study with relevance to olecranon osteotomy and fracture fixation. *J Shoulder Elbow Surg*. 2003;12:293-6.
11. Milz S, Eckstein F, Putz R. Thickness distribution of the subchondral mineralization zone of the trochlear notch and its correlation with the cartilage thickness: an expression of functional adaptation to mechanical stress acting on the humeroulnar joint. *Anat Rec*. 1997;248:189-97.
12. Wolfe S, Pederson W, Kozin S, Cohen M. Green's Operative Hand surgery. 8<sup>th</sup> ed. Philadelphia, PA, USA: Elsevier; 2021.
13. Azar FM, Canale ST, Beaty JH. Campbell's Operative Orthopaedics. 14<sup>th</sup> ed. Philadelphia, PA, USA: Elsevier.
14. Standring S. Gray's Anatomy. 42<sup>nd</sup> ed. Philadelphia, PA, USA: Elsevier; 2020.
15. Jupiter JB, Neff U, Holzach P, Allgöwer M. Intercondylar fractures of the humerus. An operative approach. *J Bone Joint Surg Am*. 1985;67:226-39.
16. Müller ME, Perren SM, Allgöwer M, Müller ME, Schneider R, Willenegger H. Manual of Internal Fixation: Techniques Recommended by the AO-ASIF group. 8<sup>th</sup> ed. Berlin, Germany: Springer Science and Business Media; 1991.
17. Cassebaum WH. Operative treatment of T and Y fractures of the lower end of the humerus. *Am J Surg*. 1952;83:265-70.
18. Henley MB. Intra-articular distal humeral fractures in adults. *Orthop Clin North Am*. 1987;18:11-23.
19. Vučinić N, Teofilovski-Parapid G, Erić M, Tubbs RS, Radošević D, Jovančević B. Morphometric analysis of the patterns of calcaneal facets for the talus in Serbian population. *PLoS One*. 2020;15:e0240818.



# In total knee arthroplasty surgeries, what is the effective dose of intra-articular tranexamic acid?

*En cirugías de artroplastia total de rodilla, ¿cuál es la dosis efectiva de ácido tranexámico intraarticular?*

Ismail G. Şahin<sup>1\*</sup> and Hüsamettin Özdemir<sup>2</sup>

<sup>1</sup>Department of Orthopaedic and Traumatology, Training and Research Hospital of Muğla Sıtkı Koçman University, Muğla; <sup>2</sup>Department of Orthopaedic and Traumatology, Edirne Sultan 1. Murat State Hospital, Edirne, Turkey

## Abstract

**Objective:** The aim of our study was to evaluate the effect of different doses of intra-articular (IA) tranexamic acid (TXA) on blood loss in total knee arthroplasty surgeries and compare it to the control group. **Materials and Methods:** A total of 160 patients who underwent unilateral total knee arthroplasty surgery at Edirne State Hospital between 2016 and 2020 were divided into four groups. The estimated blood loss and amount of blood loss from drainage, as well as transfusion rates, were compared between the groups based on surgical pre- and post-operative blood parameters to evaluate the dose effectiveness. **Results:** In our study, all TXA groups significantly reduced the estimated blood loss and amount of blood loss from drainage compared to the control group. No statistically significant difference was found between the control group and the group receiving 1 g of TXA in terms of transfusion rates ( $p = 0.062$ ), and no statistically significant difference was found between the groups receiving 2 g and 3 g of TXA. **Conclusion:** The use of 2 g of IA TXA is an effective dose for controlling blood loss in total knee arthroplasty surgeries. Lower doses do not have a significant effect on transfusion rates, whereas higher doses do not significantly increase effectiveness.

**Keywords:** Tranexamic acid. Total knee arthroplasty. Intra-articular. Topical. Local. Blood.

## Resumen

**Objetivo:** El objetivo de nuestro estudio fue evaluar el efecto de diferentes dosis de ácido tranexámico intraarticular en la pérdida de sangre en cirugías de artroplastia total de rodilla y compararlo con el grupo control. **Materiales y métodos:** La pérdida de sangre estimada y la cantidad de sangre perdida por drenaje, así como las tasas de transfusión, se compararon entre los grupos en base a los parámetros sanguíneos preoperatorios y postoperatorios quirúrgicos para evaluar la efectividad de la dosis. **Resultados:** En nuestro estudio, todos los grupos de ácido tranexámico redujeron significativamente la pérdida de sangre estimada y la cantidad de sangre perdida por drenaje en comparación con el grupo control. No se encontró diferencia estadísticamente significativa entre el grupo control y el grupo que recibió 1 g de TXA en términos de tasas de transfusión ( $p = 0.062$ ), y no se encontró diferencia estadísticamente significativa entre los grupos que recibieron 2 g y 3 g de TXA. **Conclusión:** El uso de 2 g de ácido tranexámico intraarticular es una dosis efectiva para controlar la pérdida de sangre en cirugías de artroplastia total de rodilla. Las dosis más bajas no tienen un efecto significativo en las tasas de transfusión.

**Palabras clave:** Ácido tranexámico (TXA). Artroplastia total de rodilla (TKA). Intraarticular. Tópico. Local. Sangre.

### \*Correspondence:

Ismail G. Şahin

E-mail: ismailgokhansahin@gmail.com

2444-0507/© 2023 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Date of reception: 01-01-2023

Date of acceptance: 28-07-2023

DOI: 10.24875/CIRUE.M23000750

Cir Cir (Eng). 2024;92(5):634-641

Contents available at PubMed

[www.cirugiaycirujanos.com](http://www.cirugiaycirujanos.com)



## Introduction

Osteoarthritis is a dynamic process that occurs due to the disruption of the balance between destruction and repair of the joint cartilage and subchondral bone. The goal of treatment is to improve the quality of life by reducing pain and mobility limitations and preserving or improving joint function. When conservative treatment options fail to reduce patient complaints, total knee arthroplasty surgery is currently considered the gold standard surgical treatment method, which is cost-effective and provides long-term survival. Modern total knee arthroplasty surgery began with the development of the tricompartmental total knee prosthesis by Insall and Ranawat in 1973, and the number of surgeries has increased significantly in the past 20 years.

It is reported that the average blood loss during total knee arthroplasty surgery is between 500 and 1500 mL, and the average transfusion rate is 20%, although there are also reports of average blood loss of up to 2000 mL and transfusion rates up to 50%<sup>1-4</sup>. Considering that the average blood volume in the body is approximately 5000 mL and these surgeries are often performed in the geriatric population, blood loss is a significant problem. There are several options to address this problem, including pre-operative iron replacement therapy and erythropoietin therapy; the use of pneumatic tourniquets, hypotensive anesthesia, and autologous blood transfusion during surgery; and following the flexion of the knee after surgery. The most commonly used method to replace this loss is allogeneic blood transfusion. Allogeneic blood transfusion carries the risk of allergic and immunological reactions<sup>2</sup>. There is also a risk of infection, especially in the case of viral diseases during the donor's window period. In addition, according to health-care system data, it is estimated that 2 million total knee arthroplasty surgeries will be performed in the United States in 2030, and the cost of preparing and administering one unit of allogeneic erythrocyte suspension is 250-1000 \$ (250 \$ in Turkey, 350 \$ in France, and 1000 \$ in the USA)<sup>3,5-7</sup>.

Tranexamic acid (TXA) (cyclohexanecarboxylic acid) (C<sub>8</sub>H<sub>15</sub>NO<sub>2</sub>) is a synthetic derivative of lysine and is an antifibrinolytic drug that inhibits fibrinolysis by binding to the lysine region of plasminogen<sup>4</sup>. It was first described in 1968 and has been used for the control of bleeding in gynecological and hematological diseases, among others, since 1970. It continues to

be used in a variety of indications in many fields. It has been included in the World Health Organization's list of essential drugs due to its low cost and cost-effectiveness. TXA, which has been used for the control of bleeding in various fields for many years, has become increasingly popular in the recent years in reducing blood loss associated with total knee and hip arthroplasty<sup>2-4,8-11</sup>.

There have been many meta-analyses on the effectiveness of TXA, but a consensus on the optimal dosage and mode of administration has not been reached due to the wide range of dosage and modes of administration. The effectiveness of intra-articular (IA) (topical and local) and systemic (intravenous) use of TXA in orthopedics is still controversial. Different meta-analyses have reported that the use of 1 g or more of TXA IA reduces blood loss and that the use of up to 3 g is effective and safe<sup>2,4,8-11</sup>. In addition, the IA application of TXA is an effective and practical method that allows for standard dosing independent of body weight and offers the opportunity to avoid systemic thrombotic complications (deep vein thrombosis [DVT], pulmonary embolism [PE], and venous thromboembolic event [VTE]) associated with the drug<sup>9,11,12</sup>.

There are many studies on the effect of TXA on bleeding in orthopedic prosthetic surgery, and almost all of these studies compare different methods of use with each other or with a control group. The aim of our study is to contribute to the literature by evaluating the effectiveness of IA TXA administration on blood loss and transfusion rates in total knee arthroplasty surgeries, in the same study with different doses (a total of 3 drug and 1 control groups).

## Materials and methods

This study includes data from 160 patients who underwent unilateral total knee arthroplasty for primary osteoarthritis at Edirne State Hospital between 2016 and 2020. The effective and safe dose range for IA TXA administration is 1-3 g, so the study groups were formed based on this data<sup>1-4,10-16</sup>. After a power analysis (80%), the study consisted of 40 patients each in 4 groups (IA 1 g, IA 2 g, IA 3 g, and control). Demographic data, estimated blood loss based on pre- and post-surgical blood parameters, drain blood loss, and transfusion data were compared and evaluated. The study included patients with Kellgren–Lawrence Stage 4 primary osteoarthritis, but excluded patients with secondary osteoarthritis (traumatic arthritis, inflammatory arthritis, etc.), a history of

cardiovascular treatment, more than 6 months of anti-coagulant use, and a diagnosis or suspicion of thromboembolic events.

Patients were operated on by 2 surgeons. After the surgical drape, the extremity was elevated for 10 min and wrapped with the help of Esmark bandage from distal to proximal and then inflated to 100 mmHg above the patient's systolic blood pressure and a pneumatic tourniquet was used. No patient's tourniquet pressure exceeded 300 mmHg because the surgery of patients with high systolic pressure (> 200 mmHg) was postponed. All surgeries were performed under spinal anesthesia with pneumatic tourniquet<sup>17</sup>, using the gap balancing technique<sup>18</sup> to apply a cemented posterior stabilized total knee arthroplasty (PS-TKA) (Total Knee System, Típsan, İzmir, Turkey; Knee Prosthesis System, Típméd, İzmir, Turkey). After the repair of the patellar tendon, TXA was administered to the TXA groups as a 50 mL solution with TXA (Tranexel 250 mg/5% iv/im injection Solution, Haver Farma İlaç Anonim Şirketi, İstanbul, Turkey) mixed with physiological saline (SF, 0.9% NaCl) and 50 mL SF was administered to the control group IA. After wound closure and dressing, an anti-embolism stocking was applied, and the tourniquet was released about 15 min after IA administration. The drain was clamped for 30 min after tourniquet release and the amount of blood loss from the drain was measured and recorded at 1, 3, 6, 12, 24, and 48 h, postoperatively, with the drain being removed at 48 h.<sup>16</sup> The results of the hemograms were recorded before and after surgery on the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> days. As per American society of anesthesiologists (ASA) criteria, patients with symptomatic hemoglobin (hgb) levels below 8 g/dL and all patients with hgb levels below 6 g/dL received allogeneic red blood cell suspension transfusions to raise their hgb levels to at least 10 g/dL. The estimated blood loss due to surgery was calculated using the Nadler and Gross formulas<sup>19,20</sup>. According to the Gross formula, 1 unit of red blood cell suspension is considered to be 300 mL for patients who received transfusions, which was added to the estimated blood loss.

All patients were mobilized as soon as possible, within 24 h after surgery, to prevent DVT. The patients were taught bedside foot pump and leg lift exercises and were treated with anticoagulants (0.4 mL enoxaparin and subcutaneous application) and antiembolic stockings for 20 days after surgery. The patients were mobilized and followed up after the surgery with the current rehabilitation protocol<sup>21</sup>, and the patients with

limited mobility were referred to the physical therapy and rehabilitation unit. After pain control, the patients were discharged from the hospital between the 4<sup>th</sup> and 6<sup>th</sup> days after surgery the patients were called to the outpatient clinic on the 20<sup>th</sup> day after surgery to have their sutures removed and to have their hemogram values checked.

### Statistical analysis

Statistical analyses were performed with SPSS v.23.0 software (SPSS Inc., IBM Corporation, Armonk, New York, USA). In the power analysis, it was found that, for the acceptable blood loss amount of 70 units between the treatment groups at 80% power and 5% significance level, and the standard deviation was 100, the sample size that should be included in each group was found to be 40. The groups were analyzed in terms of distribution analysis of the data and homogeneity of variance. Data with normal distribution and homogeneous variance were analyzed with parametric tests (ANOVA), and data that did not comply with normal distribution or did not have homogeneous variance were analyzed with non-parametric tests (Kruskal–Wallis, Mann–Whitney U-test). Chi-square test was used to compare categorical variables. Since there were 6 pairwise comparisons in total, Bonferroni correction was made due to group analysis, and the p-value was calculated as  $0.05/6 = 0.0083$ .

### Results

In this study, 160 patients were included, 22 of whom were male (13.75%) and 138 were female (86.25%). In 73 patients (45.63%), the right knee was operated on, and in 87 (54.37%), the left knee was operated on. The groups were compared in terms of age, height, and body weight, and no statistically significant differences were found (Table 1A).

The groups were compared in terms of ASA scores before surgery, joint range of motion measurement, surgical tourniquet time, and discharge times, and no statistically significant differences were found in any parameter (Table 1B).

The groups were compared in terms of hemoglobin (g/dL) before surgery, hematocrit (%), platelets (103/mL), and estimated body blood volume calculated according to the Nadler formula, and no statistically significant differences were found between the groups (Table 1C).

In the evaluation of post-surgical blood loss, the estimated total blood loss volume (PBL) (mL) calculated

Table 1. Whole data of the patients in 5 groups are shown

Section	Parameter	Group 4 (control)	Group 1 (IA 1GR)	Group 2 (IA 2GR)	Group 3 (IA 3GR)	p-values (p < 0.0083)
A	Age (year)	66.38 ± 8.24	66.22 ± 9.28	68.38 ± 5.19	67.32 ± 7.48	0.4332 <sup>†</sup>
	Height (cm)	164.25 ± 7.68	166.18 ± 5.70	161.68 ± 6.01	161.78 ± 6.19	0.0122 <sup>†</sup>
	Weight (kg)	81.33 ± 14.17	79.00 ± 11.35	79.80 ± 10.90	84.38 ± 12.99	0.2283 <sup>‡</sup>
	BMI (kg/m <sup>2</sup> )*	30.23 ± 5.44	28.65 ± 4.3	30.60 ± 4.41	29.41 ± 4.23	0.0113 <sup>‡</sup>
	Gender (M/F)	9/31	3/37	6/34	4/36	0.2194 <sup>§</sup>
	Side (right/left)	19/21	18/22	17/23	19/21	0.9394 <sup>§</sup>
B	ASA (I + II/III + IV)	35/5	38/2	35/5	33/7	0.2774 <sup>§</sup>
	Pre-operative ROM**	100 (85-130)	105 (75-125)	105 (70-130)	100 (80-130)	0.6102 <sup>†</sup>
	Tourniquet time (min)	100 (60-120)	100 (60-130)	105 (60-130)	105 (75-120)	0.4472 <sup>†</sup>
	Post-operative discharge day	3 (3-5)	3 (3-4)	3 (3-5)	3 (3-8)	0.1572 <sup>†</sup>
C	Hemoglobin value (g/dL)*	13.30 ± 1.20	12.79 ± 1.36	12.59 ± 1.01	12.62 ± 1.00	0.0232 <sup>†</sup>
	Hematocrit value (%)*	40.32 ± 3.54	39.26 ± 4.15	38.32 ± 2.86	38.37 ± 2.75	0.0283 <sup>‡</sup>
	Platelet count (10 <sup>9</sup> /mL)*	264.5 (153-439)	278.5 (146-519)	269 (122-512)	257.5 (142-496)	0.8642 <sup>†</sup>
	Body blood volume (l)*	3.54 ± 0.52	3.42 ± 0.39	3.45 ± 0.40	3.59 ± 0.44	0.4714 <sup>§</sup>
D	Blood transfusion ( +/ - ) (%)	9/31 (22.5%)	3/37 (7.5%)	1/39 (2.5%)	1/39 (2.5%)	0.0044 <sup>§</sup>
	Blood transfusion (count)	21	10	2	2	0.0052 <sup>†</sup>
	Blood loss from drain (mL)	649 (250-1195)	475 (200-1100)	389 (120-1100)	343 (100-1155)	0.0012 <sup>†</sup>
	Predictive blood loss (mL)	1147 (457-2533)	793 (144-2199)	729 (198-1834)	622 (129-2048)	0.0012 <sup>†</sup>
	Pbl/drain blood loss ratio	1.61 (0.53-5.03)	1.61 (0.29-5.03)	1.74 (0.3-7.26)	2.02 (0.3-5.07)	0.1332 <sup>†</sup>
E	Hemoglobin value (g/dL) <sup>§</sup>	11.00 ± 1.10	10.97 ± 0.91	11.02 ± 1.21	11.11 ± 1.05	0.9803 <sup>‡</sup>
	Hematocrit value (%) <sup>§</sup>	33.92 ± 3.45	34.27 ± 2.90	33.72 ± 3.64	33.99 ± 2.91	0.9843 <sup>†</sup>
	Platelet count (10 <sup>9</sup> /mL) <sup>§</sup>	369 (196-679)	246 (239-325)	345 (145-709)	344 (205-882)	0.3512 <sup>†</sup>

\*Preoperative.

<sup>†</sup>Kruskal Wallis.<sup>‡</sup>Anova.<sup>§</sup>Chi-square.<sup>§</sup>Postoperative 3rd week.

\*\*Range of motion.

using the Gross formula, measurement of blood loss from drains (mL), and transfusion rate (%) were used (Table 1D). In statistical analyses, statistically significant differences were found in terms of estimated blood loss, transfusion rate, and blood loss from drains (p = 0.004/0.001/0.001) (Table 1D).

The relationship between total blood loss and blood loss from drains was examined, and it was found to be 1.61 (0.53-5.07) in the control group, 1.61 (0.29-5.03) in Group 1, 1.74 (0.3-7.26) in Group 2, 2.02 (0.53-4.46) in Group 3, and 1.74 (0.29-7.26) in all patients. In the analysis, no significant difference was found between

the groups in terms of total blood loss/blood loss from the drain ratio. (p = 0.133) (Table 1D) (Fig. 1).

On the 20<sup>th</sup> day after surgery, no significant difference was found between the groups in terms of hemoglobin, hematocrit, and platelet counts (Table 1E). No deep surgical infections, PE, DVT, or VTEs were identified in the included patients.

When the groups were compared two-by-two, it was found that all TXA groups significantly reduced blood loss compared to the control group in terms of PBL (p = 0.001/0.001/0.001) and that there was no statistically significant difference between groups in terms of TXA dose (Table 2).

**Table 2. Comparison of groups in terms of predictive blood loss and drainage blood loss**

p values (p < 0.0083)	Group 4 (control)	Group 1 (IA 1GR)	Group 2 (IA 2GR)	Group 3 (IA 3GR)
Group 4	1.000*/1.000†/1.000‡	0.001§/0.001§/0.062	0.001§/0.001§/0.007§	0.001§/0.001§/0.007§
Group 1	0.001§/0.001§/0.062	1.000/1.000/1.000	0.651/0.104/0.308	0.356/0.003*/0.308
Group 2	0.001§/0.001§/0.007§	0.651/0.104/0.308	1.000/1.000/1.000	0.482/0.178/1.000
Group 3	0.001§/0.001§/0.007§	0.356/0.003§/0.308	0.482/0.178/1.000	1.000/1.000/1.000

\*Predictive blood loss.

†Drainage blood loss.

‡Allogeneic blood transfusion (%).

§Statistically significant level.

**Table 3. Comparison of groups in terms of allogeneic blood transfusion percentage and count**

p values (p < 0.0083)	Group 4 (control)	Group 1 (IA 1GR)	Group 2 (IA 2GR)	Group 3 (IA 3GR)
Group 4	1.000*/1.000†	0.062/0.133	0.007‡/0.007‡	0.007‡/0.007‡
Group 1	0.062/0.133	1.000/1.000	0.308/0.165	0.308/0.165
Group 2	0.007‡/0.007‡	0.308/0.165	1.000/1.000	1.000/1.000
Group 3	0.007‡/0.007‡	0.308/0.165	1.000/1.000	1.000/1.000

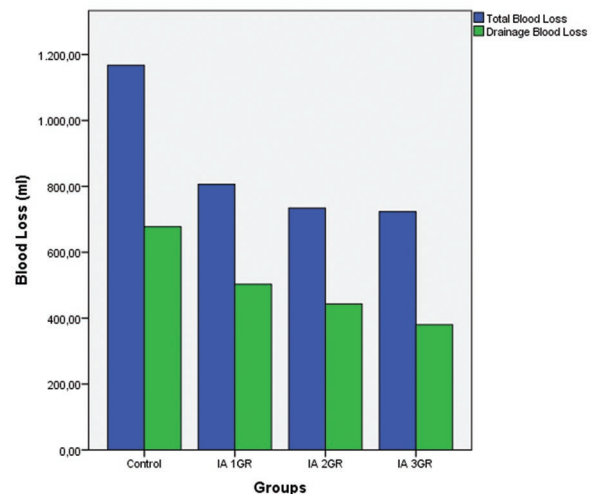
\*Allogeneic blood transfusion (%).

†Allogeneic blood transfusion (count).

‡Statistically significant level.

When the groups were evaluated in terms of transfusion rate (%), 9 patients in the control group (22.5%, 21 patients), 3 patients in the 1<sup>st</sup> group (7.5%, 10), 1 patient in the 2<sup>nd</sup> group (2.5%, 2), 1 in the 3<sup>rd</sup> group. It was determined that the patient (2.5%, 2 units) was transfused (Fig. 2). Group 1 did not create a statistically significant difference in transfusion rates compared to the control group ( $p = 0.062$ ), Groups 2 and 3 significantly reduced transfusion compared to the control group ( $p = 0.007/0.007$ ), but there was a statistically significant difference between Groups 2 and 3 ( $p = 1.000$ ) (Table 3). There was no significant difference between the control group and the first group ( $p = 0.133$ ) in the double comparisons made after the difference was detected in the comparison of the number of transfusion parameters ( $p = 0.005$ ). When compared to the control group, the number of transfusions was significantly lower in the 2<sup>nd</sup> and 3<sup>rd</sup> groups ( $p = 0.007/0.007$ ), and no significant difference was found in the two-way comparisons between the drug groups (Table 3) (Fig. 3).

When the groups were evaluated in terms of blood loss from drains, it was found that all TXA groups significantly reduced blood loss from drains compared to the control group ( $p = 0.001/0.001/0.001$ ). In

**Figure 1. Blood loss from drainage and total blood loss.**

intra-group comparisons, it was found that the application of 3 g of TXA significantly reduced blood loss from drains compared to the application of 1 g of TXA ( $p = 0.003$ ), but there was no significant difference between the application of 2 g and 3 g of TXA ( $p = 0.178$ ) (Table 2).



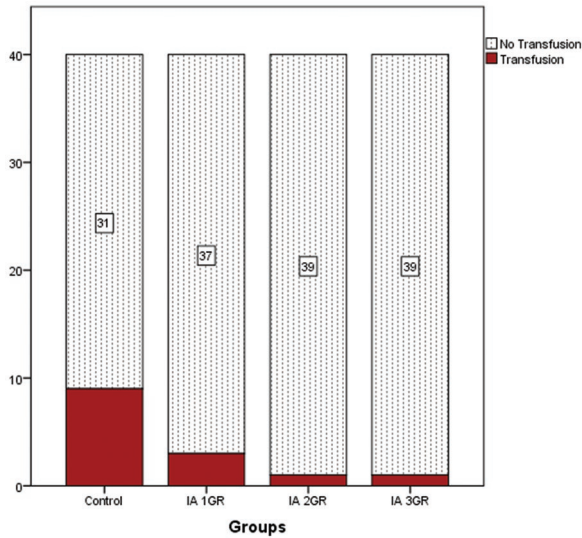


Figure 2. Allogeneic blood transfusion rates.

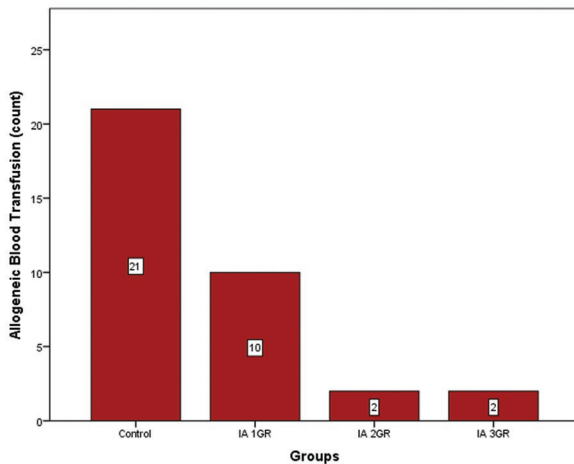


Figure 3. Allogeneic blood transfusion counts.

## Discussion

TXA is a cost-effective drug that has been used for bleeding control for approximately 50 years. There are many publications and meta-analyses stating that IA applications of TXA start to show its effect at doses of 1 g and above, and its use up to 3 g is effective and safe<sup>1-4,10-16</sup>.

A meta-analysis conducted by Xu et al. included 211 publications and found that TXA applications had lower transfusion rates compared to control groups and that IA (topical) use was a safe method in cases with high thrombosis risk<sup>11</sup>. In a study conducted by

Kim et al., 0.5, 1, 2, and 3 g IA administration doses of TXA were compared with the control group<sup>14</sup>. In this study, TXA was found to be effective in controlling bleeding at all doses of 1 g and above, and therefore it is recommended to use TXA IA in a 1 g dose. In a study by Sahin et al., the effectiveness and safety of TXA's 2 g IA use was compared with the various combinations and doses of systemic use of TXA, and it was found that IA use of 2 g was effective and safe<sup>1</sup>. In the literature, the effectiveness of TXA in IA applications below 1 g is controversial, and therefore the lowest IA TXA group in our study was taken as 1 g.

In our study, one of the most important parameters was transfusion rates. In a study conducted by Kim et al.,<sup>14</sup> different IA TXA doses were compared to a control group; a 19% transfusion rate was found in the control group, a 9% transfusion rate in the 1 g group, a 10% transfusion rate in the 2 g group, and an 8% transfusion rate in the 3 g group. In another study conducted by Sahin et al.<sup>1</sup>, the transfusion rate was found to be 17.64% in the control group and no transfusion was required in the 2 g IA TXA group (0%)<sup>1</sup>. In a study conducted by Georgiadis et al., the transfusion rate in the control group was 8%, whereas the rate in the TXA group was 0%; however, there was no statistically significant difference ( $p = 0.118$ )<sup>13</sup>. In a study by Lee et al., the transfusion rate in all groups treated with combined IA, IA + intravenous low and high doses of TXA was found to be 0%<sup>15</sup>. In our study, transfusion was performed at a rate of 22.5% in the control group, 7.5% in the 1 g TXA group, and 2.5% in both the 2 and 3 g TXA groups. Unlike the study by Kim et al.,<sup>14</sup> in our study, there was no statistically significant difference in the transfusion rates between the control group and the 1 g TXA group. In addition, there was no statistically significant difference in the transfusion rates between the 2 and 3 g TXA groups. While our transfusion rates seem to be consistent with the literature, according to the meta-analysis conducted by Mi et al., transfusion is performed in 10 g/dL or less in symptomatic patients and in 8 g/dL or less in all patients in the literature, while in our study, transfusion was limited to 8 g/dL or less in symptomatic patients, and 6 g/dL or less in all patients according to the ASA criteria and the decisions of the hospital transfusion committee<sup>2</sup>.

In our study, the estimated total blood loss due to surgery was investigated. In a meta-analysis by Moskal and Capps<sup>8</sup>, the estimated total blood loss due to surgery was found to be 834.40 mL (640.48-1028.3) in the IA TXA groups and 1195.32 mL (935.63-1455.0)

in the control groups. In a study conducted by Kim et al., TKA surgery was associated with a blood loss of  $1503 \pm 681$  mL in the control group,  $1190 \pm 379$  mL in the 1 g IA TXA group,  $1147 \pm 432$  mL in the 2 g IA TXA group, and  $1171 \pm 299$  mL in the 3 g IA TXA group, and no significant difference was found between the drug groups<sup>14</sup>. In a multicenter randomized controlled study conducted by Stowers et al.<sup>22</sup>, the blood loss in the IA 1.5 g TXA application group was 723 mL (620-826), and in the placebo group, it was 1090 mL (923-1257)<sup>21</sup>. In the study conducted by Şahin et al.<sup>1</sup>, 832 mL (403-1409) in the 2 g IA TXA group and 1309 mL (408-2119) in the control group were determined. In our study, blood loss was 1147 mL (457-2533) in the control group, 793 mL (144-2199) in the 1 g IA TXA group, 729 mL (198-1834) in the 2 g IA TXA group, and 622 mL (129-2048) in the 3 g IA TXA group. In our study, according with the literature, a significantly lower amount of bleeding was detected in the drug groups compared to the control group. However, no significant difference was found between the drug groups.

In our study, post-surgical drainage blood loss was an important parameter investigated. In a meta-analysis by Moskal and Capps<sup>8</sup>, post-operative blood loss from drains was found to be 353.69 mL (279.68-427.70) in the IA-TXA groups and 534.66 mL (410.28-659.05) in the control groups. In the study of Kim et al.,  $307.4 \pm 237.7$  mL of drainage blood loss was detected in the control group,  $259 \pm 163.4$  mL in the 1 gr IA TXA group,  $261.8 \pm 163.9$  mL in the 2 g IA TXA group, and  $258.0 \pm 110.8$  mL in the 3 g IA TXA group<sup>14</sup>. In our study, 649 mL (250-1195) of drainage blood loss was detected in the control group, 475 mL (200-1100) in the 1 g group, 389 mL (120-1100) in the 2 g group, and 343 mL (100-1155) in the 3 g group. The relationship between drainage blood loss and total blood loss was investigated and it was determined that the ratio of the amount of drainage blood loss to total blood loss was similar at a level that did not create significant differences between the groups (1.61-2.02).

One of the most significant and serious complications of TXA that has been identified in the literature is that it creates the foundation for thromboembolic events such as DVT, PE, and VTE. A meta-analysis conducted by Moskal and Capps<sup>8</sup> showed that the use of IA TXA does not increase the risk of thromboembolic interactions compared to other modes of use of TXA and that TXA is a cost-effective solution for total knee arthroplasty surgeries in centers with a transfusion rate of more than 25%. A meta-analysis

conducted by Xu et al.<sup>11</sup> found that any mode of use of TXA did not increase the risk of thromboembolic events when compared to the control group and that topical TXA application was effective and safer. A meta-analysis conducted by Mi et al.<sup>2</sup>, which analyzed the results of a total of 1308 patients showed that intravenous or IA administration of TXA did not increase the risk of thromboembolic events or deep surgical infection. Moskal and Capps<sup>8</sup> found the DVT level between 2.44% and 2.55% for the IA and control groups, and no increased risk associated with the use of TXA was found. In our study, no thromboembolic events or deep surgical infections were observed in the drug groups, consistent with the literature.

## Conclusion

In our study, we aimed to contribute to the literature by evaluating the effectiveness of IA TXA application on the amount of blood loss and transfusion rates in total knee arthroplasty surgeries, by comparing different doses proven to be effective in the same study (total of 3 drugs and 1 control group).

In our study, the use of 1 g TXA was not significantly effective when compared to the control group, and the use of 3 g TXA was not superior in any parameter in terms of the preventive effectiveness of blood loss compared to the use of 2 g TXA. According to our study, the use of more than 2 g of TXA IA did not increase the effectiveness of preventing blood loss in total knee replacement surgeries. Therefore, IA use of 2 g TXA is a cost-effective dose in total knee replacement surgeries, and no increase in anti-bleeding efficiency was found with dose increase. We concluded that the cost-effective dose to prevent bleeding in total knee replacement surgeries is 2 g and should be used at this dose.

When the meta-analyses in the literature are examined, the blood transfusion indications and the blood transfusion indications in our study are different for the reasons stated in the publication. Characteristics are an important shortcoming in the evaluation and statistical analysis of transfusion rates. In addition, the relationship between TXA use and returning to daily activities after surgery is important, and the inability to make this comparison in our study is an important shortcoming. Although no significant difference was found between the control and drug groups in terms of blood parameters taken on the 20<sup>th</sup> day in our study, more comprehensive studies are needed to evaluate the relationship between TXA and activity level in the early postoperative period.

## Funding

No financial support was received from any institution or organization during the preparation of this study.

## Conflicts of interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly, financially, or otherwise, to the subject of this article.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data, and informed consent was not required for this retrospective observational study.

## References

- Şahin İG, Akalin Y, Çevik N, Otuzbir A, Özkan Y, Öztürk A. Tranexamic acid in total knee replacement which protocol? Which application form? A prospective randomised study. *Acta Orthop Belg.* 2019;85:484-93.
- Mi B, Liu G, Zhou W, Lv H, Liu Y, Zha K, et al. Intra-articular versus intravenous tranexamic acid application in total knee arthroplasty: a meta-analysis of randomized controlled trials. *Arch Orthop Trauma Surg.* 2017;137:997-1009.
- Gillette BP, Kremers HM, Duncan CM, Smith HM, Trousdale RT, Pagnano MW. Economic impact of tranexamic acid in healthy patients undergoing primary total hip and knee arthroplasty. *J Arthroplasty.* 2013;28:137-9.
- Melvin JS, Stryker LS, Sierra RJ. Tranexamic acid in hip and knee arthroplasty. *J Am Acad Orthop Surg.* 2015;23:732-40.
- İndelen C, Uygun Kizmaz Y, Kar A, Shander A, Kirali K. The cost of one unit blood transfusion components and cost-effectiveness analysis results of transfusion improvement program. *Türk Gogus Kalp Damar Cerrahisi Derg.* 2021;29:150-7.
- Rigal JC, Riche VP, Tching-Sin M, Frontoau C, Huon JF, Cadiet J, et al. Cost of red blood cell transfusion; evaluation in a French academic hospital. *Transfus Clin Biol.* 2020;27:222-8.
- Singh JA, Yu S, Chen L, Cleveland JD. Rates of total joint replacement in the United States: future projections to 2020-2040 using the national inpatient sample. *J Rheumatol.* 2019;46:1134-40.
- Moskal JT, Capps SG. Intra-articular tranexamic acid in primary total knee arthroplasty: meta-analysis. *J Knee Surg.* 2018;31:56-67.
- Pecold J, Al-Jeabory M, Matuszewski M, Pruc M, Maslyukov A, Krupowies M, et al. Systematic review and meta-analysis of intravenous and topical tranexamic acid in reducing blood loss in knee arthroplasty. *Disaster Emerg Med J.* 2022;7:166-75.
- Tan TK, Lee JY, Tay A, Kuster M. Intra-articular versus intravenous administration of tranexamic acid in lower limb total arthroplasty: a systematic review and meta-analysis of randomised clinical trials. *Eur J Orthop Surg Traumatol.* 2022;33:709.
- Xu S, Chen JY, Zheng Q, Lo NN, Chia SL, Tay KJ, et al. The safest and most efficacious route of tranexamic acid administration in total joint arthroplasty: a systematic review and network meta-analysis. *Thromb Res.* 2019;176:61-6.
- Tammachote N, Raphiphan R, Kanitnate S. High-dose (3 g) topical tranexamic acid has higher potency in reducing blood loss after total knee arthroplasty compared with low dose (500 mg): a double-blind randomized controlled trial. *Eur J Orthop Surg Traumatol.* 2019;29:1729-35.
- Georgiadis AG, Muh SJ, Silverton CD, Weir RM, Laker MW. A prospective double-blind placebo controlled trial of topical tranexamic acid in total knee arthroplasty. *J Arthroplasty.* 2013;28:78-82.
- Kim JK, Park JY, Lee DY, Ro DH, Han HS, Lee MC. Optimal dose of topical tranexamic acid considering efficacy and safety in total knee arthroplasty: a randomized controlled study. *Knee Surg Sports Traumatol Arthrosc.* 2021;29:3409-17.
- Lee SY, Chong S, Balasubramanian D, Na YG, Kim TK. What is the ideal route of administration of tranexamic acid in TKA? A randomized controlled trial. *Clin Orthop Relat Res.* 2017;475:1987-96.
- Kim MK, Ko SH, Nam YC, Jeon YS, Kwon DG, Ryu DJ. Optimal release timing of drain clamping to reduce postoperative bleeding after total knee arthroplasty with intraarticular injection of tranexamic acid. *Medicina (Kaunas).* 2022;58:1226.
- Arthur JR, Spangehl MJ. Tourniquet use in total knee arthroplasty. *J Knee Surg.* 2019;32:719-29.
- Sheth NP, Husain A, Nelson CL. Surgical techniques for total knee arthroplasty: measured resection, gap balancing, and hybrid. *J Am Acad Orthop Surg.* 2017;25:499-508.
- Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. *Surgery.* 1962;51:224-32.
- Gross JB. Estimating allowable blood loss: corrected for dilution. *Anesthesiology.* 1983;58:277-80.
- Ekişoğlu E, Gürçay E. Total diz artroplastisi sonrası rehabilitasyon. *J İstanbul Fac Med.* 2014;76:16-21.
- Stowers MD, Aoina J, Vane A, Poutawera V, Hill AG, Munro JT. Tranexamic acid in knee surgery study-a multicentered, randomized, controlled trial. *J Arthroplasty.* 2017;32:3379-84.

# Pharyngeal mucosal closure in total laryngectomy: comparison between vertical and T-shaped closure

## *Cierre de la mucosa faríngea en la laringectomía total: comparación entre cierre vertical y cierre en T*

Adolfo Montemayor-Alatorre, Ruth P. Serna-Vazquez, Karla M. Santos-Santillana, Josefina A. Morales-del Ángel, José R. Córtes-Ponce, and José L. Treviño-González\*

Otolaryngology and Head and Neck Surgery Division, School of Medicine and University Hospital "Dr. Jose E. González", Universidad Autónoma de Nuevo León, Monterrey, Nuevo Leon, Mexico

### Abstract

**Objective:** The objective of this study was to compare the outcomes vertical and T-shaped pharyngoplasty closure techniques after total laryngectomy (TL) and to evaluate the factors associated with the development of pharyngocutaneous fistula. **Method:** We performed a retrospective study that included patients with a histopathological diagnosis of laryngeal cancer that underwent TL between 2009 and 2021. **Results:** Fifty-seven patients were included in the study. A total of 14 patients underwent a vertical closure of the neopharynx (24.6%), while 43 patients underwent a T-shaped closure (74.4%). Pharyngocutaneous fistula was the most common complication, observed in 40.4% of cases ( $n = 23$ ). No difference in the rate of complications was observed between groups, with the exception of tracheal dehiscence which was reduced in patients with T-shaped closure ( $n = 2$ , 4.7% vs.  $n = 5$ , 35.7%,  $p = 0.002$ ). Diabetes mellitus was more frequently observed in patients with the development of pharyngocutaneous fistula ( $n = 7$ , 30.4% vs.  $n = 3$ , 8.8%,  $p = 0.03$ ). **Conclusions:** Although complications were lower in the T-shaped closure group, we could not establish the superiority of either technique.

**Keywords:** Laryngectomy. Laryngeal cancer. Wound closure techniques. Fistula. Treatment outcome.

### Resumen

**Objetivo:** Evaluar los desenlaces de la técnica vertical en comparación con la técnica en T para el cierre de faringoplastia posterior a una laringectomía total, y evaluar los factores asociados con el desarrollo de fistula faringocutánea. **Método:** Estudio retrospectivo de pacientes con diagnóstico de cáncer de laringe a quienes se realizó laringectomía total como tratamiento, de 2009 a 2021. **Resultados:** Se incluyeron 57 pacientes. A 14 (24.6%) se les realizó una faringoplastia con cierre en T y a 43 (74.4%) un cierre vertical. La fistula faringocutánea fue la complicación más frecuente, presente en el 40.4% de los casos ( $n = 23$ ). No se observaron diferencias en el desarrollo de complicaciones entre grupos, con excepción de la dehiscencia traqueal, la cual fue menos frecuente en el grupo de cierre en T ( $n = 2$ , 4.7% vs.  $n = 5$ , 35.7%;  $p = 0.002$ ). La diabetes mellitus se asoció con el desarrollo de fistula faringocutánea ( $n = 7$ , 30.4% vs.  $n = 3$ , 8.8%;  $p = 0.03$ ). **Conclusiones:** Aunque se observó una tendencia a una disminución de las complicaciones en el grupo de cierre en T, no se encontró superioridad de una técnica sobre otra.

**Palabras clave:** Laringectomía. Cáncer de laringe. Técnicas de cierre quirúrgico. Fistula. Desenlace de tratamiento.

#### \*Correspondence:

José L. Treviño-González  
E-mail: jose.trevinog@uanl.mx

Date of reception: 17-06-2022

Date of acceptance: 11-07-2023

DOI: 10.24875/CIRUE.M23000751

Cir Cir (Eng). 2024;92(5):642-646

Contents available at PubMed

www.cirugiaycirujanos.com

2444-0507/© 2023 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



## Introduction

Total laryngectomy (TL) is the standard treatment for advanced laryngeal cancer and as salvage surgery after chemotherapy or radiotherapy failure<sup>1</sup>. During TL, the closure of the mucosa of the anterior wall of the pharynx is a critical step. The most common pharyngeal closure lines are vertical and T-shaped, using continuous sutures. The selection of the technique is based on the shape and size of the defect, the elasticity of the remaining tissue, and, in great part, to the preferences of the surgeon<sup>2</sup>. Few studies have evaluated the effectivity of different pharyngoplasty techniques and the reported results are controversial<sup>3</sup>.

The type of closure technique has been associated with short- and long- term complications<sup>4</sup>. Pharyngocutaneous fistulas (PCF) are the most common complication, with an incidence between 3 and 65%. The development of PCF is due in part to the dehiscence of the pharyngeal sutures and other related risk factors<sup>5</sup>. Dysphagia is also frequently observed in laryngectomized patients. The previous studies have associated the development of dysphagia with vertical pharyngeal closure<sup>6</sup>. However, evidence evaluating the patients' outcomes associated with the type of pharyngeal closure after TL is heterogeneous.

Determining the most effective technique could potentially decrease morbidity, mortality, hospitalization time, and the delay of adjuvant treatment. The objective of this study was to compare the outcomes of both vertical and T-shaped pharyngoplasty closure techniques after TL.

## Methods

We performed a retrospective study that included patients with a histopathological diagnosis of laryngeal cancer that underwent TL between 2009 and 2021 at the Otolaryngology and Head and Neck Surgery department at Hospital Universitario "Dr. José E. González". The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. This study was performed according to the principles stipulated in the Declaration of Helsinki. This project was approved by the Research and Ethics committee of our institution (reference number OT20-00010). The following data were obtained: demographic data, relevant

medical history, alcohol and tobacco use, clinical presentation, stage and localization of the tumor, primary closure technique, complications, start of oral feeding, duration of hospitalization, adjuvant treatment, and follow-up.

## Subjects

We obtained a sample of subjects over 18 years of age, with histopathological diagnosis of stage 3 or stage 4 pharyngeal carcinoma that underwent TL or salvage laryngectomy with vertical or T-shaped pharyngoplasty. The patients with a diagnosis of extrinsic larynx carcinoma, pharyngeal reconstruction with flap augmentation, a follow-up shorter than a month, presence of distant metastases, or a history of surgery for head and neck cancer were excluded.

## Study protocol

The patients were assigned to two different groups based on the surgical closure technique. All surgeries were performed by 2 surgeons (AMA and BGA). In Group 1, the technique consisted of a vertical closure of the mucosa with continuous Connel-Mayo sutures, a second layer of submucosa closure with the same sutures, and a third muscular layer closed with horizontal mattress sutures. All surgeries in group 1 were performed by AMA. In Group 2 —performed by BGA— the technique consisted in a T-shaped mucosa closure with continuous Connel-Mayo sutures, a second layer of submucosa closure with the same sutures, and a third muscular layer closed with horizontal mattress sutures. In both groups, care was taken to close the mucosa without punctures and maintaining inverted edges. In all patients, before closure, a nasogastric tube (NG) was inserted to ensure postoperative feeding and nothing by mouth was indicated.

## Statistical analysis

All analyses were performed using SPSS Statistics version 24.0 (SPSS, Inc., Armonk, NY). We obtained the frequencies and percentages for all qualitative variables. We obtained measures of central tendency and the dispersion for quantitative variables. A Pearson's chi-squared test was performed or Fisher Exact test, for 2 × 2 tables. The groups were compared according to pharyngoplasty technique. A value of  $p < 0.05$  was considered statistically significant.

## Results

### Demographic characteristics

Subject characteristics are described in table 1. Fifty-seven patients were included with a mean age of  $57 \pm 9.3$  years. A total of 14 patients underwent a vertical closure of the neopharynx (24.6%), while 43 patients underwent a T-shaped closure (74.4%). Males were the most affected sex ( $n = 52$ , 91.2%). A total of 43 (75.4%) and 48 (84.2%) had a history of alcohol consumption and tobacco use, respectively. Biomass exposure was most frequently observed in patients in the vertical closure group compared with T-shaped closure ( $n = 5$ , 37.5% vs.  $n = 2$ , 4.7%,  $p = 0.002$ ). Dysphonia was the most common symptom, observed in 54 patients (94.7%). Glottic carcinoma was the most frequently observed ( $n = 31$ , 54.4%), followed by transglottic ( $n = 25$ , 43.8%), and supraglottic ( $n = 1$ , 1.6%) carcinoma. A T4 stage was reported in most patients ( $n = 40$ , 70.2%). No patients had distance metastasis. The histopathologic report showed squamous cell carcinoma in 94.7% of the cases. Nodal metastasis was observed in 31.6% of the cases ( $n = 18$ ) and extracapsular invasion in 3.5% ( $n = 2$ ). Salvage laryngectomy was performed in 7 patients (12.3%).

### Patients' outcomes associated with closure type

Patients' outcomes are shown in table 2. All patients underwent the insertion of a NG for nutrition. A total of 10 patients (17.5%) required the use of a gastrostomy tube for adequate feeding. Intrahospitalary stay was reduced in patients with T-shaped closure compared with vertical closure, with no statistical significance ( $12.9 \pm 7.9$  vs.  $17.1 \pm 8$ ,  $p \geq 0.05$ ). PFC was the most common complication, observed in 40.4% of cases ( $n = 23$ ). No difference in the rate of complications was observed between groups, with the exception of tracheal dehiscence. Tracheal dehiscence was significantly lower in patients with T-shaped closure ( $n = 2$ , 4.7% vs.  $n = 5$ , 35.7%,  $p = 0.002$ ).

### Factors associated with the development of PCF

A total of 23 patients developed PCF (40.4%). No differences between alcohol consumption, tobacco,

**Table 1. Demographic characteristics of the studied population**

Patients' characteristics	Vertical closure	T-shaped closure	p
	(n = 14)	(n = 43)	
Age (mean, SD)	59.5 $\pm$ 9.2	59.4 $\pm$ 9.5	> 0.05
Female, n (%)	1 (7.1)	4 (9.3)	> 0.05
Alcohol consumption, n (%)	12 (85.7)	31 (72.1)	> 0.05
Alcohol consumption, grams per week	244.7 $\pm$ 382.3	368.1 $\pm$ 489.6	> 0.05
Tobacco use, n (%)	12 (85.7)	36 (83.7)	> 0.05
Tobacco use, pack year	36.1 $\pm$ 26.9	32.7 $\pm$ 36.6	> 0.05
Drug use, n (%)	1 (7.1)	5 (11.6)	> 0.05
Biomass exposure, n (%)	5 (35.7)	2 (4.7)	0.002*
Diabetes mellitus, n (%)	4 (28.6)	6 (14)	> 0.05
Hypertension, n (%)	6 (42.9)	12 (27.9)	> 0.05
Symptomatology			
Dysphonia, n (%)	14 (100)	40 (93)	> 0.05
Dyspnea, n (%)	4 (28.6)	21 (48.8)	> 0.05
Dysphagia, n (%)	2 (14.3)	14 (32.6)	> 0.05
Weight loss, n (%)	2 (14.3)	14 (32.6)	> 0.05
Need for urgent tracheostomy, n (%)	8 (57.1)	24 (55.8)	> 0.05
T stage			
T3, (%)	3 (21.4)	14 (32.6)	> 0.05
T4, (%)	11 (78.6)	29 (67.4)	> 0.05
N stage			
N0, (%)	10 (71.4)	20 (46.5)	> 0.05
N1, (%)	0 (0)	13 (30.2)	0.01*
N2, (%)	3 (21.4)	7 (16.3)	> 0.05
N3, (%)	1 (7.1)	3 (7.0)	> 0.05
Histological tumor characteristics			
Squamous cell carcinoma, n (%)	13 (92.9)	41 (95.3)	> 0.05
Nodal metastasis, n (%)	1 (7.1)	17 (39.5)	0.02*
Nodal extracapsular extension, n (%)	1 (7.1)	1 (2.3)	> 0.05
Adjuvant radiotherapy, n (%)	7 (50)	14 (32.6)	> 0.05
Adjuvant chemotherapy, n (%)	2 (14.3)	15 (34.9)	> 0.05
Salvage laryngectomy, n (%)	4 (28.6)	3 (7)	> 0.05

\* $p < 0.05$ .

SD: standard deviation.

and drug use were observed between groups. Diabetes mellitus was more frequently observed in patients with the development of PCF ( $n = 7$ , 30.4% vs.  $n = 3$ , 8.8%,  $p = 0.03$ ). Salvage laryngectomy was performed in 21.7% ( $n = 5$ ) patients with PCF compared with 5.9% ( $n = 2$ ) in patients without PCF ( $p \geq 0.05$ ). Intrahospitalary stay was significantly higher in patients

**Table 2. Patients' outcomes associated with closure type**

Outcomes	Vertical closure	T- shaped closure	p
	n = 14	n = 43	
Need for gastrostomy, n (%)	2 (14.3)	8 (18.6)	> 0.05
Initiation of oral diet (days), mean (SD)	37.6 ± 60.6	20.0 ± 19.6	0.04*
Intrahospitalary stay (days), mean (SD)	17.1 ± 8	12.9 ± 7.9	> 0.05
Complications			
PCF, n (%)	7 (50)	16 (37.2)	> 0.05
Day of diagnosis of PCF, mean (SD)	7.6 ± 17.5	3.13 ± 5.7	> 0.05
Tracheal stenosis, n (%)	4 (28.6)	6 (14)	> 0.05
Esophageal stenosis, n (%)	1 (7.1)	1 (2.3)	> 0.05
Dysphagia, n (%)	4 (28.6)	10 (23.3)	> 0.05
Wound infection, n (%)	3 (21.4)	7 (16.3)	> 0.05
Tracheal dehiscence, n (%)	5 (35.7)	2 (4.7)	0.002*

\*p&lt;0.05.

SD: standard deviation; PCF: pharyngocutaneous fistulas.

with PCF (17.1 ± 11.8 vs. 12.1 ± 3.1, p = 0.01). A higher rate of tracheal dehiscence was observed in patients with PCF (n = 6, 26.1% vs. n = 1, 2.9%, p = 0.03) (Table 3).

## Discussion

Surgical closure technique for pharyngoplasty is a determinant factor in the development of post-operative complications. A myriad of closing techniques exists, and yet there is very little literature comparing results between them. This may be due to the fact that the closing technique is not routinely specified in post-operative notes, which would impede analyses of this variable in review articles addressing PCF<sup>7</sup>.

We performed a retrospective analysis to compare two techniques of pharyngeal closure: vertical and T-shaped with continuous sutures. We found that both techniques presented similar outcomes. We observed a reduced incidence of PCF and other complications including tracheal stenosis, dysphagia, wound infection, and esophageal stenosis in patients in the T-shaped closure group. However, no statistical significance was found. Tracheal dehiscence was significantly reduced in the T-shaped closure group when compared with vertical closure. In the present study, we found an incidence of PCF similar to previous reported literature. The development of PCF was associated with a history of diabetes mellitus and with a increased postoperative intrahospitalary stay.

**Table 3. Factors associated with pharyngocutaneous fistula formation**

Evaluated variables	PCF	Non-PCF	p
	n = 23	n = 34	
Age (mean, SD)	61.1 ± 8.3	58.3 ± 9.9	> 0.05
Female, n (%)	1 (4.3)	4 (11.8)	> 0.05
Alcohol consumption, n (%)	18 (78.3)	25 (73.5)	> 0.05
Tobacco use, n (%)	19 (82.6)	29 (85.3)	> 0.05
Drug use, n (%)	2 (8.7)	4 (11.8)	> 0.05
Biomass exposure, n (%)	2 (8.7)	5 (14.7)	> 0.05
Diabetes mellitus, n (%)	7 (30.4)	3 (8.8)	0.03*
Hypertension, n (%)	10 (43.5)	8 (23.5)	> 0.05
Need for urgent tracheostomy, n (%)	14 (60.9)	18 (52.9)	> 0.05
Histological tumor characteristics			
Nodal metastasis, n (%)	6 (26.1)	12 (35.3)	> 0.05
Nodal extracapsular extension, n (%)	1 (4.3)	1 (2.9)	> 0.05
Salvage laryngectomy, n (%)	5 (21.7)	2 (5.9)	> 0.05
Intrahospitalary stay (days), mean (SD)	17.1 ± 11.8	12.1 ± 3.1	0.01
Wound infection, n (%)	7 (30.4)	3 (8.8)	> 0.05
Tracheal dehiscence, n (%)	6 (26.1)	1 (2.9)	0.03*

\*p &lt; 0.05.

SD: standard deviation; PCF: pharyngocutaneous fistulas.

Authors, such as Boltes Cecatto et al., Deniz et al., and Avci et al., evaluated the technique by focusing in the comparison of interrupted versus continuous sutures. They found that continuous sutures significantly reduce the incidence of PCF<sup>7-9</sup>. Avci et al. concluded that, aside from the type of suture used, the closing technique is also a critical factor in the development of PCF<sup>7</sup>. Davis et al. observed a higher rate of PCF formation, dysphagia, and strictures in patients in the vertical closure<sup>10</sup>. Walton et al. found that when salvage laryngectomies were excluded from their analysis, T-type closure had a lower fistula rate compared with vertical group, with no difference of postoperative strictures between groups<sup>11</sup>. However, literature remains controversial. The type of closure has been associated with the postoperative development of dysphagia and pseudo-diverticulum. Van der Kamp et al. found a greater incidence of pseudo-diverticulum in patients with vertical closure compared with T-shaped closure<sup>12</sup>. In addition, prolonged surgery time has been associated with the development of PCF; this agrees with a systematic review published by Boltes

Cecatto et al.<sup>8</sup>. Patients that underwent vertical closure had, in average, shorter surgeries and a smaller incidence of PCF.

In our study, most of the salvage laryngectomies developed PCF. In the meta-analysis published by Boltes Cecatto et al., 54% of the analyzed studies showed that pre-operative RT had a significant correlation with the development of PCF<sup>8,13</sup>. Liang et al. reported a greater incidence of PCF in patients that underwent RT (21.2%) compared with patients that did not undergo RT (11.6%)<sup>14</sup>.

We observed a 40% overall incidence of PCF with no difference between the closure technique used. The overall incidence of PCF after TL is heterogeneous, being from 11.2% to 34.8% depending on the assessed literature<sup>14,15</sup>. Several risk factors for the development of PCF have been studied, being a history of previous radiotherapy one of the most important<sup>13</sup>. Other associated risk factors include advanced age, history of smoking, preoperative albumin and hemoglobin, T stage, tumor site, and among others<sup>13</sup>. We hypothesize that the tumor size in our population played a major role for high incidence of PCF in patients without a history of radiotherapy. Despite considered T4a in TNM staging and candidates for surgical management, we commonly observed local advanced disease with high tumor burdens which influence at the time of reconstruction and pharyngeal closure.

The main strength of this paper is that each closure technique was performed by a single surgeon, with an identical surgical protocol between the patients of each group. The main limitations are the retrospective aspect of our study, and the relatively small sample size.

## Conclusion

The pharyngeal vertical and T-shaped closure techniques using uninterrupted Connel-Mayo sutures show similar efficacy. Although complications were lower in the T-shaped closure group, we could not establish the superiority of either technique. Further studies with larger sample sizes are needed to develop a better understanding of the importance of the closure technique for pharyngoplasty and to find the technique associated with better surgical outcomes.

## Funding

The authors declare that they have not received funding.

## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical disclosures

**Protection of humans and animals.** The authors declare that no experiments on humans or animals were performed for this research.

**Confidentiality of data.** The authors declare that they have followed their center's protocols on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

## References

1. Thompson CS, Asimakopoulos P, Evans A, Vernham G, Hay AJ, Nixon IJ. Complications and predisposing factors from a decade of total laryngectomy. *J Laryngol Otol*. 2020;134:256-62.
2. Rassekh CH, Haughey BH. Total laryngectomy and laryngopharyngectomy. In: Cummings Otolaryngology Head and Neck Surgery. 6th ed. Philadelphia, PA: Saunders Elsevier; 2015. p. 1699-713
3. Haksever M, Akduman D, Aslan S, Solmaz F, Ozmen S. Modified continuous mucosal connell suture for the pharyngeal closure after total laryngectomy: zipper suture. *Clin Exp Otorhinolaryngol*. 2015;8:281-8.
4. Walton B, Vellucci J, Patel PB, Jennings K, McCammon S, Underbrink MP. Post-laryngectomy stricture and pharyngocutaneous fistula: review of techniques in primary pharyngeal reconstruction in laryngectomy. *Clin Otolaryngol*. 2018;43(1):109-116.
5. Iglesias-Moreno MC, Gimeno-Hernández J, Gómez-Serrano M, Carricondo F, Gil-Loyzaga P, Poch-Broto J. Pharyngo-cutaneous fistula: an old problem revisited. *Acta Otolaryngol*. 2011;131:1311-8.
6. Watkinson JC, Gilbert RW. Stell and Maran's Textbook of Head and Neck Surgery and Oncology. 5th ed. Boca Raton: Taylor and Francis Group; 2012.
7. Avci H, Karabulut B. Is it important which suturing technique used for pharyngeal mucosal closure in total laryngectomy? Modified continuous connell suture may decrease pharyngocutaneous fistula. *Ear Nose Throat J*. 2020;99:664-70.
8. Cecatto SB, Soares MM, Henriques T, Monteiro E, Moura CI. Predictive factors for the postlaryngectomy pharyngocutaneous fistula development: systematic review. *Braz J Otorhinolaryngol*. 2014;80:167-77.
9. Deniz M, Ciftci Z, Gultekin E. Pharyngoesophageal suturing technique may decrease the incidence of pharyngocutaneous fistula following total laryngectomy. *Surg Res Pract*. 2015;2015:363640.
10. Davis RK, Vincent ME, Shapshay SM, Strong MS. The anatomy and complications of "T" versus vertical closure of the hypopharynx after laryngectomy. *Laryngoscope*. 1982;92:16-22.
11. Walton B, Vellucci J, Patel PB, Jennings K, McCammon S, Underbrink MP. Post-laryngectomy stricture and pharyngocutaneous fistula: review of techniques in primary pharyngeal reconstruction in laryngectomy. *Clin Otolaryngol*. 2018;43:109-16.
12. Van der Kamp MF, Rinkel RN, Eerenstein SE. The influence of closure technique in total laryngectomy on the development of a pseudo-diverticulum and dysphagia. *Eur Arch Otorhinolaryngol*. 2017;274:1967-73.
13. Wang M, Xun Y, Wang K, Lu L, Yu A, Guan B, et al. Risk factors of pharyngocutaneous fistula after total laryngectomy: a systematic review and meta-analysis. *Eur Arch Otorhinolaryngol*. 2020;277:585-99.
14. Liang JW, Li ZD, Li SC, Fang FQ, Zhao YJ, Li YG. Pharyngocutaneous fistula after total laryngectomy: a systematic review and meta-analysis of risk factors. *Auris Nasus Larynx*. 2015;42:353-9.
15. Mattioli F, Bettini M, Molteni G, Piccinini A, Valoriani F, Gabriele S, et al. Analysis of risk factors for pharyngocutaneous fistula after total laryngectomy with particular focus on nutritional status. *Acta Otorhinolaryngol Ital*. 2015;35:243-8.



# Does the sonic hedgehog signaling pathway play a role in anti-reflux mechanism of bladder in children?

*¿La vía de señalización de sonic hedgehog desempeña un papel en el mecanismo antirreflujo de la vejiga en los niños?*

Eda Tokat<sup>1\*</sup>, Mustafa O. Tan<sup>2</sup>, and Serhat Gürocak<sup>2</sup>

<sup>1</sup>Department of Urology, University of Health Sciences, Ankara Research and Training Hospital; <sup>2</sup>Section of Paediatric Urology, Department of Urology, Gazi University School of Medicine. Ankara, Turkey

## Abstract

**Objective:** A hedgehog family ligand, namely, sonic hedgehog (SHH), was reported to be important in the development of bladder and ureter smooth muscle. In this prospective study, we aimed to determine protein expression of SHH in resected ureterovesical junction (UVJ) segments of children with vesicoureteral reflux (VUR). **Materials and Methods:** The study group included 19 children; 12 (63%) girls, 7 (37%) boys, who had ureteroneocystostomy operation; 3 (15.7%) right sided, 7 (36.8%) left sided, 9 (47.3%) bilateral, due to primary VUR between years 2015 and 2018. Totally, 28 UVJ segments were examined for Western Blot analysis to determine related protein expression levels. **Results:** The mean Western blot band area of SHH gene pathway related protein was 3880.69 (2059.55-13941.61) while the mean area of  $\beta$ -Actin, the house-keeping gene, was 20180.25 (9530.39-26709.75) ( $p = 0.001$ ). Correlation analyses between grade of reflux and protein expression of SHH gene pathways revealed no significant relation ( $p = 0.300$ ). When the UV samples were grouped as low- and high-grade reflux and compared in terms of SHH protein expression levels, no statistically significant difference was found between groups ( $p = 0.818$ ). **Conclusion:** We concluded that SHH signaling molecule which is effective in development of bladder and ureter smooth musculature might also be effective in etiopathology of reflux.

**Keywords:** Sonic hedgehog. Vesicoureteral reflux. Reflux genetics. Bladder development.

## Resumen

**Objetivo:** Se ha informado que el ligando sonic hedgehog (SHH) es importante en el desarrollo de los músculos lisos de la vejiga y el uréter. Nuestro objetivo fue determinar la expresión proteica de SHH en los segmentos de la unión ureterovesical de niños con reflujo vesicoureteral (RVU). **Materiales y Métodos:** El grupo de estudio incluyó a 19 niños; 12 (63%) niñas, 7 (37%) niños, que tuvieron operación de ureteroneocistostomía (UNC); 3 (15.7%) derecho, 7 (36.8%) izquierdo, 9 (47.3%) bilateral, por RVU primario entre los años 2015-2018. Se examinaron un total de 28 segmentos de la unión ureterovesical para análisis de transferencia Western para determinar los niveles de expresión de proteínas relacionadas en las muestras. **Resultados:** El área media de la banda de transferencia Western de la proteína relacionada con la vía del gen SHH fue de 3880.69 (2059.55-13941.61), mientras que el área media de la  $\beta$ -actina, el gen de limpieza, fue de 20180.25 (9530.39-26709.75) ( $p = 0.001$ ). Los análisis de correlación entre el grado de reflujo y la expresión de proteínas de las vías del gen SHH no revelaron una relación significativa ( $p = 0.300$ ). **Conclusión:** Concluimos que la molécula de señalización SHH también podría ser efectiva en la etiopatología del reflujo vesicoureteral.

**Palabras clave:** Erizo sónico. Reflujo vesicoureteral. Genética del reflujo. Desarrollo de la vejiga.

### \*Correspondence:

Eda Tokat

E-mail: edatokat@gmail.com

Date of reception: 16-12-2022

Date of acceptance: 22-02-2023

DOI: 10.24875/CIRUE.M23000752

Cir Cir (Eng). 2024;92(5):647-651

Contents available at PubMed

www.cirugiaycirujanos.com

2444-0507/© 2023 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

The non-physiologic retrograde flow of urine from the bladder to kidneys is defined as vesicoureteral reflux (VUR), with 1-2% prevalence and in some children has a genetic predisposition<sup>1</sup>. The triangular region between two ureterovesical junctions (UVJs) and internal ureteral meatus, namely, “the bladder trigone” has a central importance in anti-reflux mechanism and was found to derive mostly from bladder muscle with the contribution of ureteral fibers. This was approved in animal studies by the presentation of two major muscle types in the trigone; detrusor and the muscles associated with the intramural ureter<sup>2</sup>. The cellular morphology of the trigone depends on both its embryological origin and key signaling molecules including sonic hedgehog (SHH) signaling<sup>2,3</sup>. During bladder development, the smooth muscle of bladder differentiates from primitive mesenchyme under the influence of urothelium and a sufficient concentration of SHH was reported to be important in development of bladder smooth musculature<sup>4-7</sup>. Patched (Ptc 1), the membrane bound receptor for SHH is expressed in embryonic bladder mesenchyme. Ptc 1 suppresses the smoothened (Smo) in unbound state and when the SHH binds Ptc 1, this inhibitory effect disappears and initiates the cascade which activates Gli transcription factors (Gli1, Gli 2 and Gli 3) in target cell<sup>8</sup>. Gli1 and Gli 2 are the ones targeting not only the SHH but also Wnt family and bone morphogenic proteins which play role in normal embryonic development and differentiation<sup>5</sup>.

The UVJ avoids retrograde flow of urine from the variable pressure bladder to low pressure upper urinary tract (kidney and ureter) depending on the ureteral musculature at the junction particularly. Proper development of ureteral and trigonal musculature ensures this one-way flow. In case a deficiency occurs in trigonal development, some clinical disorders including VUR might occur due to improper muscle formation resulting in a relatively short intramural tunnel<sup>4</sup>. In this regard, we hypothesized that the defective SHH signaling plays a role in development of VUR due to abnormal trigonal/ureteral musculature and aimed to determine protein expression of this gene in resected UVJ segments of children with VUR. In this prospective study, we aimed to determine protein expression of SHH in resected UVJ segments of children with VUR and to our knowledge, this is the first

human study trying to highlight the role of SHH protein expression in reflux etiopathogenesis.

## Materials and Methods

### *Study design and sample preparation*

This prospective study was approved by the Institutional Ethical Committee and informed consent was obtained from all the patients/parents before their inclusion in the study. (26.02.2018/161).

The study group included 19 children; 12 (63%) girls, 7 (37%) boys, who had ureteroneocystostomy (UNC) operation; 3 (15.7%) right-sided, 7 (36.8%) left-sided, 9 (47.3%) bilateral, due to primary VUR between years 2015 and 2018. The technique of UNC was Cohen in all patients and renal units except one unilateral operation done by the Politano-Leadbetter combined intra and extravesical technique. The hypoplastic and redundant distal ureter was excised and the excised hypoplastic distal segment including the intramural portion was used for the genetic analyses. Finally, a total of 28 UVJ segments were examined for Western Blot analysis to determine related protein expression level of SHH gene signaling pathway in the UVJ specimens. After the appropriate transport of the materials to the laboratory, protein isolation was carried out for each tissue and preserved at  $-80^{\circ}\text{C}$  for later analysis. Protein concentrations were determined in all samples using Qubit® Protein Assay Kits (Thermo Fisher Scientific, Cat No: Q33211). Western blot band expression levels of housekeeping gene  $\beta$ -Actin and target gene SHH which is thought to be effective in VUR pathogenesis were transformed into numerical data using Image J program (NIH, Bethesda, MD, USA).

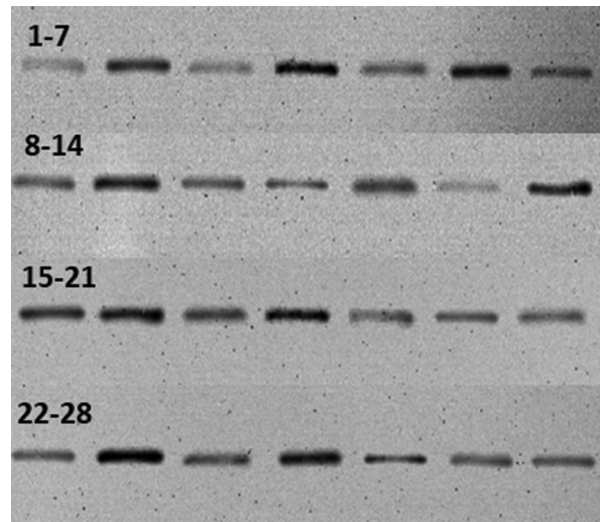
Housekeeping genes are known to be expressed in almost all the cells of an organism and generally considered to be the constitutive genes which are essential for the maintenance of the basic cellular functions<sup>9</sup>. In this respect, housekeeping genes are widely used as internal controls for gene expression normalization for analysis as western blotting, northern blotting, RT-PCR, etc.<sup>10</sup>. Therefore, in this study, mean abundance values of SHH protein were calculated and compared with  $\beta$ -actin for each related tissue thus expression levels of Western blot bands were normalized against  $\beta$ -actin. Clinical parameters of the patients enrolled in our study were also retrospectively reviewed.

## Western blotting

For protein denaturation, we used 100 µg from each sample and also added 4× NuPAGE LDS sample buffer (thermo fisher scientific, Cat no: NP0004) (5 µL), 10× NuPAGE sample reducing agent (thermo fisher scientific, Cat no: B0004) (2 µL) and distilled water was added to a total volume of 20 µL. This mixture was incubated at 70°C for 10 min and ice cooled for 2 min. 20 µL (100 µg) quantities of prepared protein were loaded and separated by 12% SDS-PAGE (Invitrogen, NuPAGE 4-12% Bis-Tris Gel, Cat: NP0321PK2), then transferred to a polyvinylidene difluoride membrane. Following blocking with 5% bovine serum albumin (5%BSA) in phosphate buffered saline with 0.1% tween 20 (PBS-T), the membrane was incubated overnight at 4°C with rabbit Anti-SHH Antibody (St. John's Laboratory, Cat: STJ193168) and rabbit anti-β-actin antibody (St. John's laboratory, Cat: STJ91464) as the loading control. Primary antibodies were diluted in 1:500 (anti-SHH) and 1:1000 (anti-β-actin). For the secondary incubation, membranes underwent hybridization with a horseradish peroxidase (HRP)-conjugated goat-anti-rabbit-IgG antibody (1:10000 dilution; advansta, Cat no: R05072-500) for 1 h at room temperature. After washing 3 times in PBS/0.1% tween 20, proteins were visualized in imaging system (ChemiDoc-It<sup>2</sup>, UVP) with using 6 ml NZY supreme enhanced chemiluminescent HRP substrate (Nzytech, Cat no: Mb19301) (Fig. 1).

## Statistical analysis

Densitometry of the Western Blot protein bands was analyzed using Image J (NIH, Bethesda, MD, USA) software program. Statistical analyses were applied with the (Statistical Package for Social Sciences, Chicago, IL, USA) version 15.0 program. Descriptive analyses were presented as mean ± standard deviation and median (min-max). Normal distribution of data was analyzed using Shapiro–Wilk test ( $p \leq 0.05$ ) and non-parametric tests were used for additional statistics then. Densitometry of the target protein (SHH) band was compared to the house keeping gene, β-actin with Wilcoxon test and groups according to the grade of reflux (low-high), laterality, presence of scar and differential functions ( $< 40\%$ - $\geq 40\%$ ) were compared using Mann–Whitney U test. Correlation analyses were applied to test the relation between grade of VUR and protein expression level.  $p \leq 0.05$  was considered as statistically significant.



**Figure 1:** Sonic hedgehog protein western blot band view of renal units.

## Results

The mean age and follow-up duration of the patients were  $88.6 \pm 47.7$  and  $26.76 \pm 16.6$  months, respectively. According to “International Reflux Grading System” 14 (50%) renal units were grouped as low-grade reflux (Grades 1-3) while 14 (50%) renal units were in high-grade reflux group (Grades 4, 5). No family history of reflux was recorded in the patients included in this study. Of the 19 patients with 28 renal units, six patients with 12 units (42.9%) had bilateral and 9 patients with 9 units (32.1%) had unilateral scar formation on DMSA scintigraphy. Renal units were also grouped according to differential functions ( $\geq 40\%$  and  $< 40\%$ ) obtained by renal scintigraphy and then compared in terms of protein expressions. In this series, the differential renal function was  $< 40\%$  in 14 (50%) renal units whereas  $\geq 40\%$  in the other 14 (50%).

The mean western blot band area of SHH gene pathway-related protein was 3880.69 (2059.55-13941.61) while the mean area of β-actin, the house-keeping gene, was 20180.25 (9530.39-26709.75) ( $p = 0.001$ ). Correlation analyses between grade of reflux and protein expression of SHH gene pathway revealed no significant relation ( $p = 0.30$ ). When the UV samples were grouped as low- and high-grade reflux and compared in terms of SHH protein expression levels, no statistically significant difference was found between reflux groups ( $p = 0.818$ ). Analysis comparing the specimens according to presence of scar formation revealed no statistically significant difference in terms of SHH protein

**Table 1. Sonic hedgehog protein band area calculations according to convenient groups**

Classification groups for analysis	Number of contents (renal unit) (%)	SHH protein median western blot band area (min-max)	p*
Low-grade reflux	14 (50)	4405.04 (2059.55-12515.64)	0.818
High-grade reflux	14 (50)	3280.69 (2169.98-13941.61)	
Unilateral reflux	10 (35.7)	3284.28 (2169.98-10296.55)	0.314
Bilateral reflux	18 (64.3)	4546.74 (2059.55-13941.61)	
Bilateral scar formation	21 (75)	4296.57 (2059.55-13941.61)	0.915
Unilateral scar formation	7 (25)	3103.74 (2746.96-13941.61)	
≥ 40% differential function	14 (50)	3083.86 (2059.55-13941.61)	1
< 40% differential function	14 (50)	4405.04 (2169.98-12515.64)	

\*p ≤ 0.05 is statistically significant.

expression (p=0.915). In addition, there was no statistically significant difference between ≥ 40% and < 40% function groups regarding SHH band area (p = 1). As stated before 9 (47.3%) patients had bilateral reflux whereas 10 (52.7%) had unilateral VUR in this series. In case of the possible impact of bilaterality on the results, the two groups were compared and no statistically difference was found with respect to SHH protein expression between groups (p = 0.314) (Table 1).

## Discussion

In the recent study, we found that SHH protein expression levels significantly decreased in the hypoplastic UVJ segments of the patients with VUR. On the other hand, our results did not reveal a relationship between the level of expression and severity of reflux or kidney status.

At the early gestational week 12, the condensate myoblasts of distal ureter convert into smooth muscle fibrils. These longitudinal smooth muscle fibers place at the dorsal wall of the bladder before reaching the orifice. These small diameter muscle fibrils merge the opposite fascicles and create the interureteral muscle and mucosal fold between two ureteric orifices at gestational week 14. The hypothetical function of the intertrigonal muscle is moving the two orifices medially and downward with a periodic contraction and providing a passive antireflux mechanism by the prolongation of intramural ureter<sup>11</sup>. Some studies suggested that the intramural tunnel of ureters compose of bladder muscles and develop independent from the ureters even if in the absence of a ureter, though the mechanism still remains unclear<sup>2,12</sup>. As mentioned above, the muscle development of distal

ureteric segments is in mesh with bladder. The development of ureter and trigon musculature is proven to be essential to provide the one-way flow of urine from the ureters into bladder and to prevent the kidneys from reflux of urine or bacteria<sup>4</sup>. Because it is thought that trigon musculature deficiencies result in relatively short intramural tunnel.

A hedgehog family ligand, namely, SHH, controls cell fate, cell differentiation, and proliferation in embryogenesis<sup>7,13</sup>. In the literature, numerous studies have reported the SHH and its downstream signaling molecules produced by the developing bladder epithelium to have a key role in development and patterning of bladder smooth muscle and otherwise cause the bladder development to fail<sup>5-7,14,15</sup>. Histological studies indicated that either SHH or an intact urothelium is necessary to induce smooth muscle differentiation, thus the source of SHH is thought to be the urothelium<sup>8</sup>. When SHH signaling molecule binds with the transmembrane receptor Patched (Ptch), this activation causes depression of Smo and activates the Gli transcription factors in the target cell to involve in bladder development and differentiation<sup>15</sup>.

However, several studies reported that high concentrations of SHH inhibit the smooth muscle differentiation while they agreed that lower concentrations induce this process<sup>6,7,16</sup>. Cheng et al. reported that Gli2, one of the target transcription factors of SHH, upregulates the Bmp4 expression and inhibits the smooth muscle differentiation<sup>6</sup>. Another study carried out by Shiroyanagi et al. also supported the information that SHH acts as both an inducer and an inhibitor of bladder smooth muscle differentiation<sup>5</sup>.



Our results were in the same direction that SHH is required for normal development of musculature of ureter and trigone and the depressed levels of regarding protein might cause VUR. The insignificant relationship between the severity of reflux and protein expression levels might have occurred due status of other related signaling factors or downstream molecules functionary in this pathway. Furthermore, different expression levels of SHH might cause inhibition or activation and might have varied through years. All the patients were postnatally diagnosed so that there was no investigation about the Shh protein deficiency prenatally through gestational weeks. Although this is the first study in human examining the related protein expression in ureteral specimens, our study has two limitations. First, for ethical reasons, it was not possible to establish a control group to compare the expression levels of Shh protein in normal ureteral tissue. Normal ureteral tissue could be obtained from nephrectomy materials performed with another diagnosis, but this was not possible in our study group because they were pediatric patients. Therefore, further studies with an appropriate control group are needed to address this issue. The second one is relatively small sized study group to generalize our results to overall VUR patients. To the best of our knowledge, our study retains its value to be the first human study aiming to find the effect of SHH signaling pathway in VUR etiopathogenesis.

## Conclusions

SHH signaling pathway which is effective in the development of bladder and ureter smooth musculature might also be effective in etiopathology of VUR. Further studies with appropriate control groups will be precious to prove our results and contribute to the diagnosis and treatment of VUR.

## Funding

This study is supported by Gazi University Scientific Research Projects Unit with the project coded 01/2019-22.

## Conflicts of interest

No potential conflicts of interest were reported by the authors.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

## References

- Slabbaert K, Bogaert G. Vesicoureteric reflux (VUR) in children: where are we now. *Arch Esp Urol*. 2012;65:450-8.
- Viana R, Baturina E, Huang H, Dressler GR, Kobayashi A, Behringer RR, et al. The development of the bladder trigone, the center of the anti-reflux mechanism. *Development*. 2007;134:3763-9.
- Yu J, Carroll TJ, McMahon AP. Sonic hedgehog regulates proliferation and differentiation of mesenchymal cells in the mouse metanephric kidney. *Development*. 2002;129:5301-12.
- Liaw A, Cunha GR, Shen J, Cao M, Liu G, Sinclair A, et al. Development of the human bladder and ureterovesical junction. *Differentiation*. 2018;103:66-73.
- Shiroyanagi Y, Liu B, Cao M, Agras K, Li J, Hsieh MH, et al. Urothelial sonic hedgehog signaling plays an important role in bladder smooth muscle formation. *Differentiation*. 2007;75:968-77.
- Cheng W, Yeung CK, Ng YK, Zhang JR, Hui CC, Kim PC. Sonic hedgehog mediator Gli2 regulates bladder mesenchymal patterning. *J Urol*. 2008;180:1543-50.
- Haraguchi R, Motoyama J, Sasaki H, Satoh Y, Miyagawa S, Nakagata N, et al. Molecular analysis of coordinated bladder and urogenital organ formation by Hedgehog signaling. *Development*. 2007;134:525-33.
- Tasian G, Cunha G, Baskin L. Smooth muscle differentiation and patterning in the urinary bladder. *Differentiation*. 2010;80:106-17.
- Zhu J, He F, Hu S, Yu J. On the nature of human housekeeping genes. *Trends Genet*. 2008;24:481-4.
- Lin J, Redies C. Histological evidence: housekeeping genes beta-actin and GAPDH are of limited value for normalization of gene expression. *Dev Genes Evol*. 2012;222:369-76.
- Oswald J, Schwentner C, Lunacek A, Fritsch H, Longato S, Sergi C, et al. Reevaluation of the fetal muscle development of the vesical trigone. *J Urol*. 2006;176:1166-70.
- Wang GJ, Brenner-Anantharam A, Vaughan ED, Herzlinger D. Antagonism of BMP4 signaling disrupts smooth muscle investment of the ureter and ureteropelvic junction. *J Urol*. 2009;181:401-7.
- Ericson J, Muhr J, Jessell T, Edlund T. Sonic hedgehog: a common signal for ventral patterning along the rostrocaudal axis of the neural tube. *Int J Dev Biol*. 2003;39:809-16.
- Jenkins D, Winyard PJ, Woolf AS. Immunohistochemical analysis of Sonic hedgehog signalling in normal human urinary tract development. *J Anat*. 2007;211:620-9.
- DeSouza KR, Saha M, Carpenter AR, Scott M, McHugh KM. Analysis of the Sonic hedgehog signaling pathway in normal and abnormal bladder development. *PLoS One*. 2013;8:e53675.
- Cao M, Tasian G, Wang MH, Liu B, Cunha G, Baskin L. Urothelium-derived Sonic hedgehog promotes mesenchymal proliferation and induces bladder smooth muscle differentiation. *Differentiation*. 2010;79:244-50.

# Solid pseudopapillary neoplasia of the pancreas: incidental finding with increased frequency

## *Neoplasia sólida pseudopapilar de páncreas: hallazgo incidental cada vez más frecuente*

Inés Cañas-García\*, Clotilde Moreno-Cortés, Enrique Dabán-Collado, and Benito Mirón-Pozo

Servicio de Cirugía General y Aparato Digestivo, Hospital Clínico San Cecilio, Granada, Spain

### Abstract

*In the context of cystic lesions of the pancreas and their paucisymptomatic symptoms, we present the case of a 33-year-old woman with epigastric pain and nonspecific abdominal discomfort. Computed tomography and magnetic resonance imaging were performed, with the finding of a lesion at the level of the head-uncinate process of the pancreas, compatible with a solid pseudopapillary neoplasm of the pancreas. The procedure was performed with a cephalic pancreaticoduodenectomy of Whipple, without incident. After 18 months of follow-up, the disease remains free. It is worth highlighting the importance of images prior to therapeutic planning, due to the proximity of the tumor to the celiac artery in the hepatic artery's origin.*

**Keywords:** Neoplasia. Pseudopapillary. Pancreas.

### Resumen

*En el contexto de las lesiones quísticas del páncreas y su clínica paucisintomática, se presenta el caso de una mujer de 33 años que inicia estudio por epigastralgia y molestias abdominales. Se realizan tomografía computarizada y resonancia magnética, con hallazgo de una lesión a nivel de la cabeza-proceso uncinado del páncreas, compatible con una neoplasia pseudopapilar sólida del páncreas. Se interviene realizando duodenopancreatectomía cefálica de Whipple, que transcurre sin incidencias. Tras 18 meses de seguimiento, persiste libre de enfermedad. Cabe destacar la importancia de las imágenes previas a la planificación terapéutica, por la proximidad de la tumoración al tronco celíaco en la salida de la arteria hepática.*

**Palabras clave:** Neoplasia. Pseudopapilar. Páncreas.

#### \*Correspondence:

Inés Cañas-García

E-mail: inescanasgarcia@gmail.com

2444-0507/© 2022 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Date of reception: 23-09-2021

Date of acceptance: 07-01-2022

DOI: 10.24875/CIRUE.M22000753

Cir Cir (Eng). 2024;92(5):652-654

Contents available at PubMed

[www.cirugiaycirujanos.com](http://www.cirugiaycirujanos.com)

## Introduction

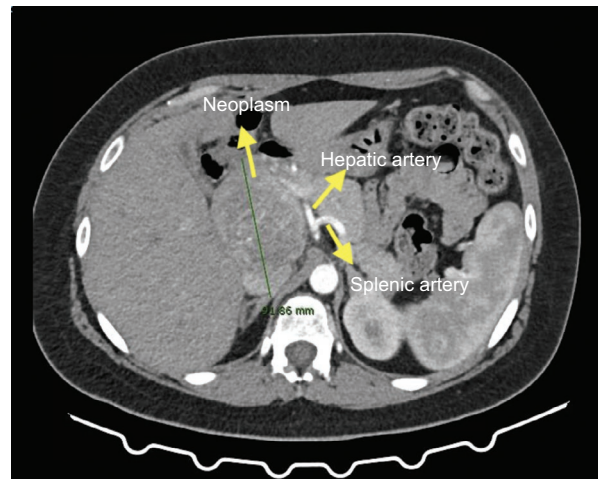
This is the case of a 33-year-old woman with nonspecific abdominal pain whose radiologic findings revealed a cystic tumor in the pancreas. Supplementary testing suggests a solid pseudopapillary neoplasm of the pancreas. This type of lesion frequently affects young women, with a typical location in the neck and tail of the pancreas, is considered premalignant, and has a potential for metastasis in up to 15% of cases.<sup>1,2</sup> Consequently, an accurate differential diagnosis is crucial to plan appropriate treatment. The uniqueness of this case lies in the rare location of the lesion in the head of the pancreas and its proximity to surrounding structures (hepatic artery exiting the celiac trunk and the ampulla of Vater), which required an aggressive surgical approach involving a Whipple cephalic duodenopancreatectomy.

## Case report

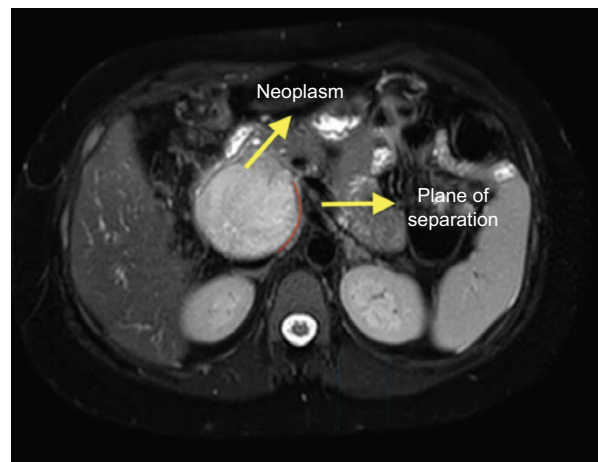
A 33-year-old woman with no previous past medical history presented with epigastric pain, diarrhea, early satiety, and abdominal distension. Lab test results revealed normal tumor markers. Multiphase contrast-enhanced computed tomography (CT) (Fig. 1) and magnetic resonance imaging (MRI) (Fig. 2) identified a lesion at the head-uncinate process of the pancreas, hypointense on T1 and hyperintense on T2, with a maximum diameter of 92 mm, without biliary tract dilation, distal glandular atrophy, or distant lesions. A solid pseudopapillary neoplasm of the pancreas was suspected. Surgery was performed, revealing a large tumor; enucleation was not performed due to involvement of the duodenal papilla, and a Whipple cephalic duodenopancreatectomy was performed (Fig. 3). Pathological examination confirmed resection with clear margins, without lymphatic, vascular, or perineural invasion. The patient completed the postoperative period without complications and was discharged on day 9. Eighteen months after surgery, she remains disease-free.

## Discussion

Distinguishing the clinical and radiological characteristics of pancreatic cystic neoplasms is essential for differential diagnosis, as it can guide us in choosing the optimal therapeutic approach. The incidence of pancreatic cystic neoplasms has increased due to the rise in imaging modalities performed for other reasons, with an estimated prevalence of up to 8% in

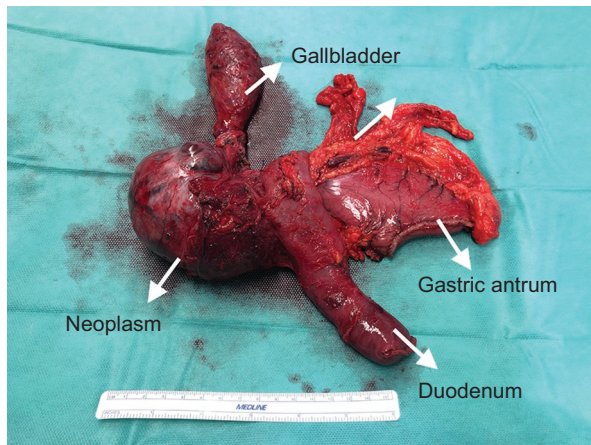


**Figure 1.** Mass of 92 mm anteroposterior diameter, originating from the pancreatic head, adjacent to the celiac trunk and hepatic artery, surrounding them without infiltration.



**Figure 2.** T2-phase magnetic resonance imaging showing a hyperintense mass surrounded by a pseudocapsule, with a separation plane from adjacent structures.

the population.<sup>1</sup> Differential diagnosis can have significant therapeutic implications: history-taking, including assessment of alcohol intake, the presence of cholelithiasis, the history of abdominal trauma, and particularly acute or chronic pancreatitis, are critical factors in suspecting malignancy.<sup>2,3</sup> Contrast-enhanced CT and MRI with cholangiopancreatography sequences are ideal imaging modalities to evaluate the characteristics of the pancreatic duct, the presence or absence of glandular atrophy, and possible involvement of the biliary tract, as well as to better characterize cystic lesions.<sup>4</sup> The role of endoscopic ultrasound lies in its superior sensitivity for detecting



**Figure 3.** Surgical specimen. Cephalic duodenopancreatectomy.

small periampullary and pancreatic lesions. Additionally, it enables the evaluation of anatomical relationships around the lesion and allows for biopsy sampling for pathological examination and marker analysis, such as carcinoembryonic antigen or amylase.<sup>5</sup>

Solid pseudopapillary neoplasms of the pancreas predominantly affect young women, with an incidence reaching up to 2% in some series. Generally, they are asymptomatic and are detected due to symptoms related to compression of neighboring organs, commonly located in the body-tail of the pancreas.<sup>6,7</sup> These tumors exhibit typical imaging features on CT and MRI; in MRI T2-phase, they appear as hyperintense masses surrounded by a pseudocapsule.

They show expansive growth but rarely infiltrate, and are considered borderline due to their metastatic potential.<sup>8</sup> Despite this, the prognosis is very favorable if resected in early stages. Surgical resection is thus recommended once a suspected diagnosis is established, particularly for lesions > 5 cm or near the head and uncinate process of the pancreas.<sup>9</sup> Poor prognostic factors include perineural invasion, vascular invasion, and the presence of nodal or extrapancreatic metastases, typically in the liver.

## Conclusions

The uniqueness of this case lies in the location of the lesion in the pancreatic head and its proximity to

vascular structures and the duodenal papilla, which precluded conservative resection, requiring an aggressive surgical approach to achieve total lesion removal.

## Funding

The authors declare that they have not received funding.

## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

## References

1. Yamaue H, Tanimura H, Shono Y, Onishi H, Tani M, Yamoto H, et al. Solid and cystic tumor of the pancreas: clinicopathologic and genetic studies of four cases. *Int J Pancreatol.* 2000;27:69-76.
2. Salinas W, Marani M, Reimondez S, Alcaraz A, Signorini F, Maraschio M, et al. Solid pseudopapillary neoplasm of the pancreas. *Cir Cir.* 2021;89:263-8.
3. Charville GW, Kao CS. Serous neoplasms of the pancreas. *Arch Pathol Lab Med.* 2018;142:1134-40.
4. Llatas J, Palomino A, Frisancho O. Tumor de Frantz: neoplasia sólida pseudopapilar de páncreas. *Rev Gastroenterol Peru.* 2011;31:56-60.
5. Fong ZV, Ferrone CR, Lillemoe D, Fernández del Castillo C. Intraductal papillary mucinous neoplasm of the pancreas. Current state of the art and ongoing controversies. *Ann Surg.* 2016;263:908-17.
6. Frago R, Fabregat J, Jorba R, García-Borobia F, Altet J, Serrano MT, et al. Solid pseudopapillary tumors of the pancreas: diagnosis and curative treatment. *Rev Esp Enferm Dig.* 2006;98:809-16.
7. Cienfuegos JA, Rotellar F, Ruiz-Canela M. Neuroendocrine tumors of the pancreas: keys issues in dealing with heterogeneity. *Rev Esp Enferm Dig.* 2017;109:672.
8. Jorba R, Fabregat J, Borobia FG, Busquets J, Ramos E, Torras J, et al. Neoplasias quísticas del páncreas. Manejo diagnóstico y terapéutico. *Cir Esp.* 2008;84:296-306.
9. Busquets J, Fabregat J, Jorba R, Borobia FG, Valls C, Serrano T, et al. Indicaciones y resultados de la cirugía conservadora en las lesiones localizadas en la cabeza pancreática. *Cir Esp.* 2007;82:105-11.



# Report of two cases of high cervical injury: an adequate functional result with timely surgical management

*Reporte de dos casos de lesión cervical alta: un resultado funcional adecuado con manejo quirúrgico oportuno*

Antonio Sosa-Nájera<sup>1</sup>, Abrahan A. Tafur-Grandett<sup>2\*</sup>, Alejandro Ceja-Espinosa<sup>1</sup>, Raúl Huato-Reyes<sup>1</sup>, and Jorge Ortega-Espino<sup>2</sup>

<sup>1</sup>Department of Neurosurgery, Grupo Neurológico de Alta Especialidad, Hospital Ángeles Morelia, Morelia, Michoacán; <sup>2</sup>Department of Neurosurgery, Centro Médico "Lic. Adolfo López Mateos", Instituto de Salud del Estado de México, Toluca, Estado de México. Mexico

## Abstract

**Introduction:** Odontoid fractures correspond to 9-15% of cervical spine fractures. Atlas fracture is rare (3-13%)<sup>8</sup>. **Case presentation:** Male with Anderson and D'Alonzo Type II Odontoid fracture with unstable fragment treated with occipitocervical fixation with occipital plate, C2-C3 transfacet screws; Female with type E Jefferson fracture + anterolateral atlaoaxial dislocation, treated with occipitocervical fixation, C2-C3-C4 transfacet screws. **Discussion:** Anderson and D'Alonzo Type II fractures and Jefferson type E fractures are a surgical emergency due to instability and neurological deficit.

**Keywords:** Type II odontoid fracture. Jefferson fracture. Spinal cord trauma. Occipitocervical fixation. Posterior cervical instrumented fusion.

## Resumen

**Introducción:** Las fracturas odontoideas corresponden del 9-15% de las fracturas de la columna cervical. La fractura del atlas es poco común (3-13%)<sup>8</sup>. **Presentación del caso:** Masculino con fractura de Odontoides tipo II de Anderson y D'Alonzo con fragmento inestable tratado con fijación occipitocervical con placa occipital, tornillos transfacetarios C2-C3; Femenino con fractura de Jefferson tipo E + luxación atloaxoidea anterolateral, tratada con fijación occipitocervical, tornillos transfacetarios C2-C3-C4. **Discusión:** Fracturas tipo II de Anderson y D'Alonzo y fracturas de Jefferson tipo E son una urgencia quirúrgica debido a inestabilidad y déficit neurológico.

**Palabras clave:** Fractura de odontoides tipo II. Fractura de Jefferson. Traumatismo Raquimedular. Fijación occipitocervical. Fusión cervical posterior.

### \*Correspondence:

Abrahan A. Tafur Grandett  
E-mail: atafur.grandett@hotmail.com

Date of reception: 08-09-2021

Date of acceptance: 21-10-2021

DOI: 10.24875/CIRUE.M21000754

Cir Cir. 2024;92(5):655-660

Contents available at PubMed

www.cirugiaycirujanos.com

2444-0507/© 2021 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Odontoid fractures correspond to 9-15% of cervical spine fractures<sup>1</sup>. Of these, the Anderson and D'Alonzo Type II fracture is the most common and occurs in more than 60% of cases<sup>2</sup>. These are usually the result of high energy trauma, such as car accidents or falls from height, most of them are associated with a head injury to the frontal region that indirectly produces an extension injury and predominates in males<sup>3</sup>.

According Anderson and D'Alonzo, these fractures can be classified as: Type I: Fracture of the odontoid apex, Type II: Fracture of the odontoid base, Type III: Vertebral body fracture, and Type II odontoid fractures (T II-OF) can be treated surgically or conservatively<sup>1,4</sup>.

Various treatments have been proposed for TII-OF with the aim of reducing fracture fragments, stabilizing the fracture, allowing fusion, and reducing pain<sup>5</sup>. In general, the treatment of patients with a fracture of the odontoid process is based on the type of fracture, the age of the patient, the patient's health, the relationship with neurological deficits, and personal preference of the surgeon. Relative indications for surgery include fracture dislocation > 5 mm, angulation > 10 and failed attempts at closed reduction. Surgical treatment may involve anterior odontoid screw fixation or posterior atlantoaxial arthrodesis, resulting in stabilization of the upper cervical spine<sup>5,6</sup>.

In cases with indication for surgery for surgery, the purpose of the intervention will be: (A) to release trapped root elements through discectomies, corpectomies, laminectomies, evacuation of collections of expansion of spaces, (B) align vertebral segments by compass or halo traction, manipulation or surgery, (C) stabilize vertebral elements with surgical techniques via anterior, posterior or with double 360° approaches, and (D) stop the clinical-radiological evolution, (E) allow maximum functional recovery<sup>7</sup>. Atlas fracture is rare, accounting for 3-13% of all cervical spine fractures and 1.3-2% of all spinal injuries<sup>8,9</sup>. Unstable atlas fracture is even rare and is mainly caused by vertical falls, traffic accidents and other vertical traumatic forces<sup>9</sup>. Atlas fractures were classified by Jefferson in 1920, into seven types (Table 1)<sup>10</sup>.

Jefferson Type E fracture is very dangerous, as displacement of bone blocks can cause spinal cord injury, leading to serious complications such as paraplegia and death.

Therefore, the stability of the atlantoaxial complex must be reconstructed surgically. Treatment is aimed

**Table 1. Jefferson Classification of Atlas fractures**

Type	Anatomical diagnosis
A	Unilateral or bilateral anterior arch fracture
B	Unilateral or bilateral posterior arch fracture
C	Simple fracture of a lateral mass
D	Comminuted lateral mass fracture (the TLA is possibly damaged)
E	True Jefferson fracture in which the anterior and posterior arches of the atlas are fractured bilaterally (unstable atlas fracture)
F	Linear or crossed unilateral anterior arch and posterior arch fractures
G	Isolated TLA break

TLA: transverse ligament of the atlas.

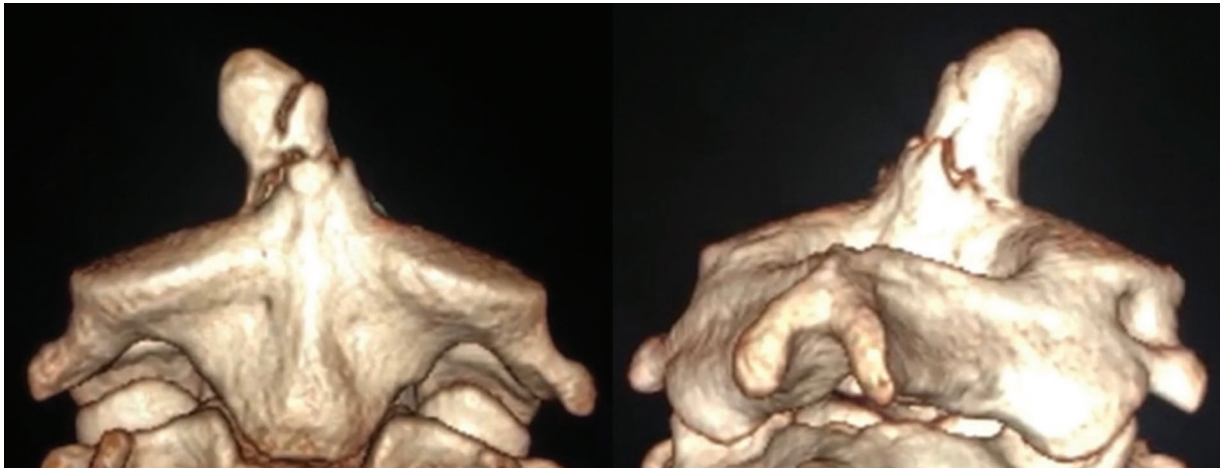
at correcting the dislocation, restoring stability to the atlantoaxial joint, and retaining the maximum degree of motion of the cervical spine<sup>9</sup>.

## Case presentation

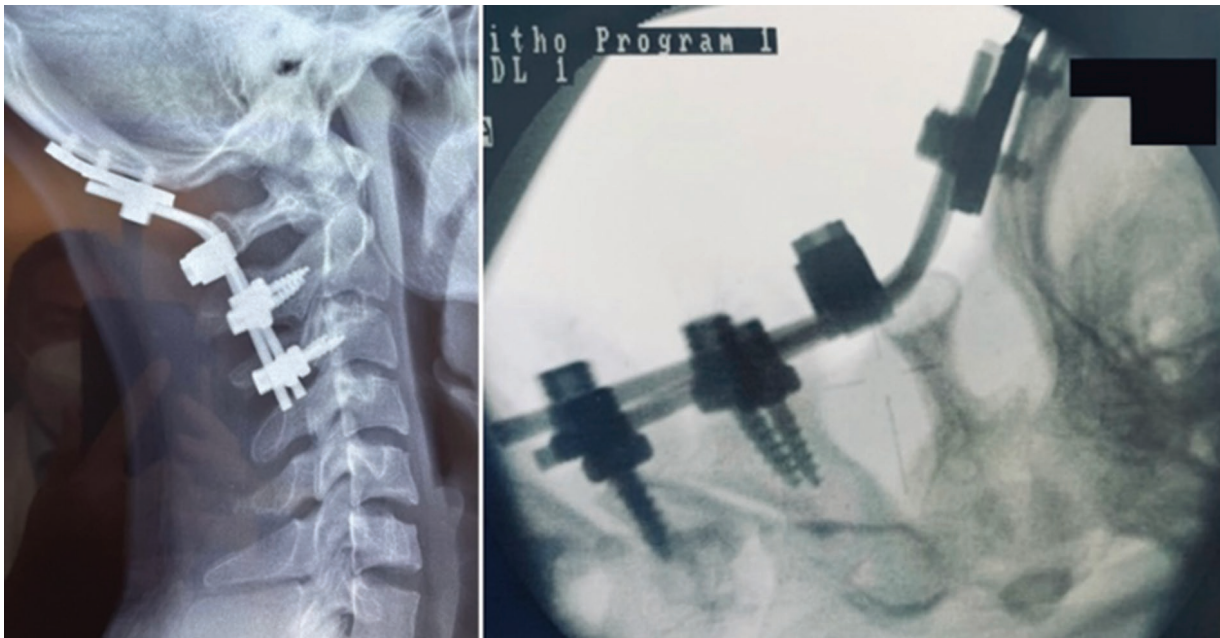
The first case is a 20 years old male who suffers direct head trauma when diving into a pool exerting direct axial force on the cervical spine, refers to paresthesia in upper limbs at the time of trauma, denies loss of alertness, as well as epileptic seizures, 15 points in the Glasgow Coma Scale, motor and sensory system without alterations, global ++/+++ muscle stretch reflexes, intact posterior cords, and multiple SCALP- type cranial vault wounds.

Simple tomography of normal skull and simple crane cervical tomography with 3D reconstruction showing Anderson and D'Alonzo Type II odontoid fracture with unstable left fragment and risk of posterior displacement (Fig. 1). An urgent decision was made to perform a posterior approach for occipitocervical fixation with occipital plate, 4 C2-C3 polyaxial trans facet screws, titanium bars, and Cross Link and subsequent placement of rigid Aspen-type collar (Fig. 2).

The second case is a 29 years old female who has a fall of approximately 6 m in height, exerting vertical force on the cervical spine, refers to a sudden decrease in force in both thoracic limbs, denies other symptoms. To the neurological examination with a 15 points in the Glasgow Coma Scale, motor system with force 3/5 on the Daniels scale C5, C6, C7, and C8 myotomes, sensory without alterations, intact posterior cords, global ++/+++ muscle stretch reflexes



**Figure 1.** 3D reconstruction of craniocervical CT with Anderson and D'Alonzo Type II odontoid fracture with unstable left fragment and posterior displacement.



**Figure 2.** Occipitocervical fixation with occipital plate, four poly axial trans facet screws C2 C3, titanium bars, and Cross Link.

craniocervical computerized tomography showing Type E Jefferson fracture + anterolateral atloaxial dislocation (Fig. 3).

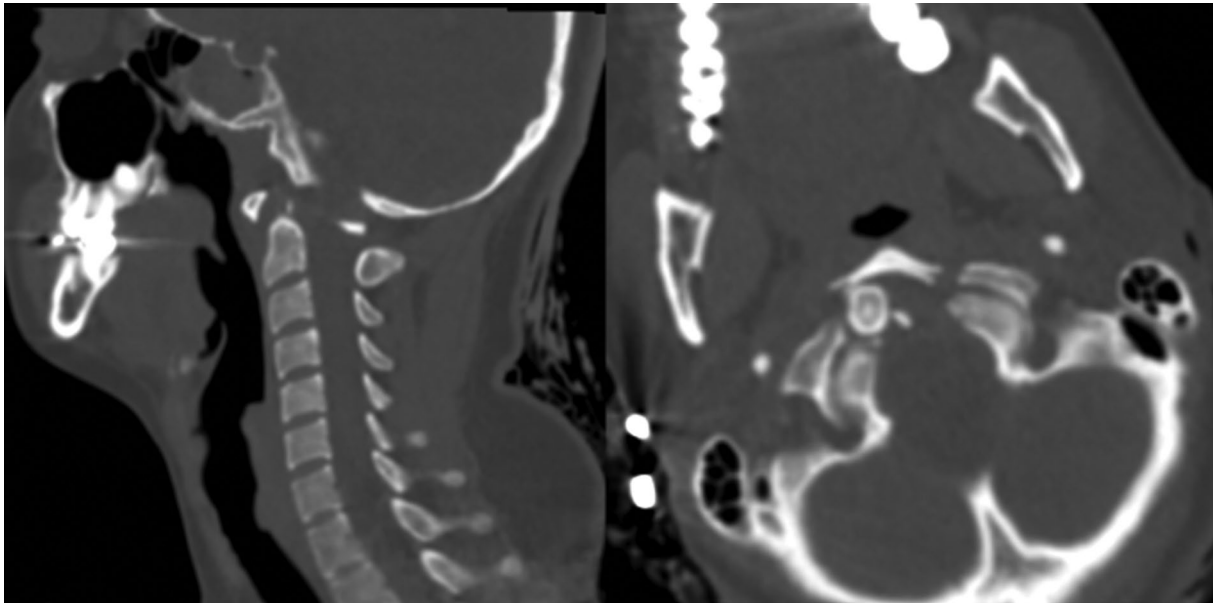
It was to decide to perform a posterior approach with occipitocervical fixation with an occipital plate, six polyaxial trans facet screws of C2-C3-C4, titanium bars, and Cross Link and subsequent placement of a rigid Aspen-type collar (Fig. 4).

Both patients in the post-operative period without added neurological deficit, presenting reversal of symptoms on admission, with control radiological

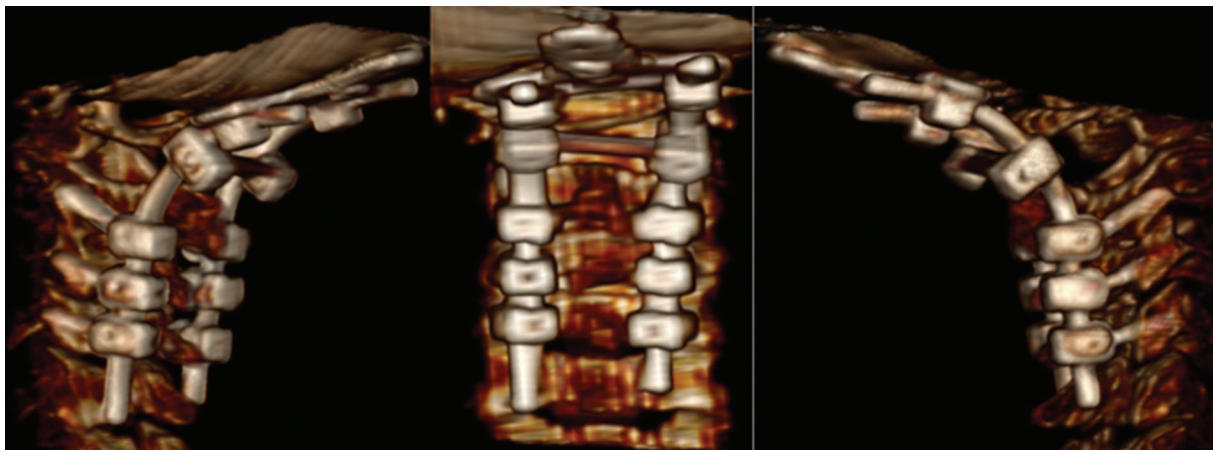
studies with adequate placement of prosthetic material, returned home 2 days after the operation (Fig. 5).

## Discussion

Odontoid fractures are often caused by high energy trauma, such as fall from a height and traffic accidents<sup>11-13</sup>. Represent 9-15% of all cervical fractures. These injuries are believed to be extremely dangerous due to the potential risk of upper cervical cord injury after traumatic instability. The distribution of odontoid



**Figure 3.** Craniocervical TC scans showing type E Jefferson fracture + anterolateral atlantoaxial dislocation.



**Figure 4.** Occipitocervical fixation with an occipital plate, six polyaxial trans facet screws C2-C3-C4, titanium bars, and Cross Link.

fractures according to age shows two peaks, one in younger patients (17-30 years), associated with high energy trauma, the other peak occurs in geriatric patients (> 70 years old) and is associated with low energy trauma, such as falls<sup>1,14,15</sup>.

Although the majority of patients arriving at the hospital will not have a noticeable neurologic injury, a detailed neurologic evaluation is required, as displaced fracture fragments can compress the spinal cord and lead to cervical myelopathy. In a review of 446 T II-OF, Przybylsky found that 82% of the patients were neurologically intact, 8% had minimal sensory disturbances in the scalp or extremities and 10% had significant neurological deficits<sup>16</sup>. However, in a retrospective analysis

of 16 patients with neglected odontoid fractures, Crockard et al.<sup>1</sup> found that all patients had neck pain at 1 year and 69% had clinical signs of myelopathy, including upper extremity weakness and gait disturbances<sup>1,7</sup>.

Acceptable options for the initial treatment of all types of odontoid fractures include external cervical immobilization with a hard cervical collar, whereas Type II fractures should be considered for surgical fixation in the context of a 5 mm displacement, communication, Type IIA, and inability to achieve/maintain fracture alignment with external immobilization<sup>3</sup>.

Surgeons appear to recognize morbidity as an important factor during the decision-making process and have concluded that morbidity is not an absolute





**Figure 5.** Post-surgical result without neurological deficit, with adequate ranges of mobility in cervical flexion and extension, strength 5/5 on the Daniels scale in all four extremities.

contraindication to surgery. The morbidity that is relevant for surgery is also relevant for non-surgical treatment<sup>1</sup>.

Jefferson fractures are associated with other traumatic cervical injuries in up to 50% of cases, most commonly with posteriorly displaced T II-OF<sup>17,18</sup>. Unstable Jefferson fractures are characterized by a tear of the transverse ligament of the atlas (TLA), resulting in lateral displacement of the lateral masses after excessive axial loading<sup>18,19</sup>.

At present, the treatment of C1 fractures remains controversial and there are no internationally accepted standards of treatment. For isolated atlas fractures, conservative treatment is the main method, but for unstable atlas fractures, surgical treatment remains the preferred method. It is widely accepted that surgery is indicated for atlas fracture associated with atlantooccipital instability, intraligamentous rupture of the TLA, and for “unstable” atlas fracture<sup>9,20,21</sup>.

Anderson and D’Alonzo T II-OF and Jefferson type E fractures are a surgical emergency due to the potential for instability, they present and the secondary

neurological deficit for the patient requesting to generate quadriplegia, high cervical injury with ascending spinal cord edema and secondary bulbar injury, cardiorespiratory arrest, and even death, surgical treatment must be individualized for each patient and according to the surgeon’s expertise.

The cure rate for T II-OF (with an age range of 18–64 years) treated with posterior atlantoaxial fixation is relatively high<sup>22</sup>.

Decision-making for odontoid fracture is challenging and requires careful consideration of many factors related to the nature of the fracture and the patient. The selection of the fixation procedure requires a thorough understanding of the patient’s anatomy and careful preparatory evaluation and planning for successful treatment and favorable clinical outcomes<sup>3</sup>.

For Jefferson Type E fractures occipitocervical fixation combined with short-term external immobilization establishes upper cervical stability and prevents further spinal cord injury and damage to nerve function<sup>18</sup>.

Occipitocervical fusion with transpedicular fixation has the advantages of reliable fixation, few complications, and high fusion rates<sup>9</sup>.

The most important point of treatment for atlantoaxial fracture is to reduce and stabilize the injured segment to prevent further neurological injury. The TLA frequently causes severe instability of the upper cervical spine.

Surgical treatment is always necessary for patients combined with bilateral anterior and posterior arch fractures, and unstable fractures with lesion of the TLA<sup>23,24</sup>.

## Funding

The authors declare no funding was received.

## Conflicts of interest

The authors declare that there are no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

## References

1. Falavigna A, Righesso O, Da Silva PG, Siri CR, Daniel JW, Veiga JC, et al. Management of Type II odontoid fractures: experience from Latin American spine centers. *World Neurosurg.* 2017;98:673-81.
2. Fiumara E, Tumbiolo S, Lombardo MC, Maugeri R, Porcaro S, Gioia F, et al. Type II Odontoid Fracture: a case series highlighting the treatment strategies. *Acta Neurochir Suppl.* 2019;125:317-24.
3. Carvalho AD, Figueiredo J, Schroeder GD, Vaccaro AR, Rodrigues-Pinto R. Odontoid fractures: a critical review of current management and future directions. *Clin Spine Surg.* 2019;32:313-23.
4. Patel AA, Lindsey R, Bessey JT, Chapman J, Rampersaud R, Spine Trauma Study Group. Surgical treatment of unstable Type II odontoid fractures in skeletally mature individuals. *Spine (Phila Pa 1976).* 2010;35:S209-18.
5. Clark CR, White AA 3<sup>rd</sup>. Fractures of the dens. A multicenter study. *J Bone Joint Surg Am.* 1985;67:1340-8.
6. Grasso G, Leone L, Torregrossa F. Management of odontoid cervical fracture. *World Neurosurg.* 2019;123:246-7.
7. Ochoa G. Surgical management of odontoid fractures. *Injury.* 2005;36 Suppl 2:B54-64.
8. Kandziora F, Chapman JR, Vaccaro AR, Schroeder GD, Scholz M. Atlas fractures and atlas osteosynthesis: a comprehensive narrative review. *J Orthop Trauma.* 2017;31:S81-9.
9. Guo W, Lin Y, Huang J, Hu F, Ding Z, Xiao Z, et al. Treatment strategy of unstable atlas fracture: a retrospective study of 21 patients. *Medicine (Baltimore).* 2020;99:e20153.
10. Jefferson G. Fracture of the atlas vertebra. Report of four cases and a review of those previously recorded. *Br J Surg.* 2005;7:407-22.
11. Ni B, Guo Q, Lu X, Xie N, Wang L, Guo X, et al. Posterior reduction and temporary fixation for odontoid fracture: a salvage maneuver to anterior screw fixation. *Spine (Phila Pa 1976).* 2015;40:E168-74.
12. Ryken TC, Hadley MN, Aarabi B, Dhall SS, Gelb DE, Hurlbert RJ, et al. Management of isolated fractures of the axis in adults. *Neurosurgery.* 2013;72 Suppl 2:132-50.
13. Hadley MN, Dickman CA, Browner CM, Sonntag VK. Acute axis fractures: a review of 229 cases. *J Neurosurg.* 1989;71:642-7.
14. Subach BR, Morone MA, Haid RW Jr., McLaughlin MR, Rodts GR, Co-mey CH. Management of acute odontoid fractures with single-screw anterior fixation. *Neurosurgery.* 1999;45:812-9; discussion 819-20.
15. Lee PC, Chun SY, Leong JC. Experience of posterior surgery in atlanto-axial instability. *Spine (Phila Pa 1976).* 1984;9:231-9.
16. Butler JS, Dolan RT, Burbridge M, Hurson CJ, O'Byrne JM, McCormack D, et al. The long-term functional outcome of Type II odontoid fractures managed non-operatively. *Eur Spine J.* 2010;19:1635-42.
17. Levine AM, Edwards CC. Fractures of the atlas. *J Bone Joint Surg Am.* 1991;73:680-91.
18. Hu Y, Yuan ZS, Kepler CK, Dong WX, Sun XY, Zhang J. Comparison of occipitocervical and atlantoaxial fusion in treatment of unstable Jefferson fractures. *Indian J Orthop.* 2017;51:28-35.
19. Kontautas E, Ambrozaitis KV, Kalesinskas RJ, Spakauskas B. Management of acute traumatic atlas fractures. *J Spinal Disord Tech.* 2005;18:402-5.
20. Hein C, Richter HP, Rath SA. Atlantoaxial screw fixation for the treatment of isolated and combined unstable Jefferson fractures-experiences with 8 patients. *Acta Neurochir (Wien).* 2002;144:1187-92.
21. Mead LB 2<sup>nd</sup>, Millhouse PW, Krystal J, Vaccaro AR. C1 fractures: a review of diagnoses, management options, and outcomes. *Curr Rev Musculoskelet Med.* 2016;9:255-62.
22. Huang DG, Zhang XL, Hao DJ, He BR, Wang XD, Liu TJ. The healing rate of Type II odontoid fractures treated with posterior atlantoaxial screw-rod fixation: a retrospective review of 77 patients. *J Am Acad Orthop Surg.* 2019;27:e242-8.
23. Cao L, Yang E, Xu J, Lian X, Cai B, Liu X, et al. "Direct vision" operation of posterior atlantoaxial transpedicular screw fixation for unstable atlantoaxial fractures: a retrospective study. *Medicine (Baltimore).* 2017;96:e7054.
24. Takayasu M, Aoyama M, Joko M, Takeuchi M. Surgical intervention for instability of the craniocervical junction. *Neurol Med Chir (Tokyo).* 2016;56:465-75.

# Mixed adenoneuroendocrine carcinoma: case report

## *Carcinoma adenoneuroendocrino mixto: reporte de caso*

Ángel A. Hernández-Moreno<sup>1\*</sup>, Carlos E. Durón-Gutiérrez<sup>2</sup>, Sheyla P. Serrano-González<sup>2</sup>, Grettel León-Martínez<sup>3</sup>, and José G. Arroyo-Del-Castillo<sup>4</sup>

<sup>1</sup>Servicio de Cirugía Plástica y Reconstructiva, Hospital Regional Lic. Adolfo López Mateos, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE); <sup>2</sup>Servicio de Cirugía General, Hospital General Tacuba, ISSSTE; <sup>3</sup>Servicio de Anatomía Patológica, Hospital General Tacuba, ISSSTE; <sup>4</sup>Servicio de Neurocirugía, Instituto Nacional de Neurología y Neurocirugía, Secretaría de Salud de la Ciudad de México. Mexico City. Mexico

### Abstract

**Introducción:** Mixed adenoneuroendocrine carcinoma is a rare tumor of the gastrointestinal tract with double differentiation into adenomatous and neuroendocrine carcinoma, each component with at least 30%. **Case report:** A 60-year-old female with acute abdominal pain. Surgical treatment was decided, finding a tumor at the level of the cecum and ascending colon, a right hemicolectomy and ileostomy were performed. **Discussion:** Mixed adenoneuroendocrine carcinoma can appear in various organs. They are highly malignant tumors, with a high risk of metastasis. **Conclusions:** These tumors do not present symptoms or specific radiological or laboratory findings; diagnosis depends on postoperative histopathological and immunohistochemical studies.

**Keywords:** Mixed adenoneuroendocrine carcinoma. Adenocarcinomatous differentiation. Neuroendocrine differentiation. Colorectal cancer.

### Resumen

**Introducción:** El carcinoma adenoneuroendocrino mixto es un tumor raro del tracto gastrointestinal con doble diferenciación en carcinoma adenomatoso y neuroendocrino, cada componente con al menos el 30%. **Caso clínico:** Mujer de 60 años con cuadro de dolor abdominal agudo. Se decide tratamiento quirúrgico, encontrando un tumor a nivel de ciego y colon ascendente, y se realizan hemicolectomía derecha e ileostomía. **Discusión:** El carcinoma adenoneuroendocrino mixto puede aparecer en diversos órganos. Son tumores muy malignos, con alto riesgo de metástasis. **Conclusiones:** Estos tumores no presentan síntomas ni hallazgos radiológicos o de laboratorio específicos; el diagnóstico depende de estudios histopatológicos e inmunohistoquímicos posoperatorios.

**Palabras clave:** Carcinoma adenoneuroendocrino mixto. Diferenciación adenocarcinomatosa. Diferenciación neuroendocrina. Cáncer colorrectal.

#### \*Correspondence:

Ángel A. Hernández-Moreno

E-mail: dr.alexhmoreno@gmail.com

Date of reception: 16-09-2021

Date of acceptance: 14-03-2022

DOI: 10.24875/CIRUE.M22000755

Cir Cir (Eng). 2024;92(5):661-664

Contents available at PubMed

www.cirugiaycirujanos.com

2444-0507/© 2022 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Mixed adenoneuroendocrine carcinoma (MANEC) is a rare GI tract tumor with dual adenocarcinomatous and neuroendocrine differentiation, with each component representing at least 30% of the tumor<sup>1</sup>. Although rare, these tumors exhibit aggressive behavior and generally indicate a poor prognosis. Standardizing treatment for MANECs has historically been challenging due to a lack of diagnostic histological classification. Due to its rarity, current treatment recommendations for mixed adenoneuroendocrine carcinoma are based on limited data and generally follow guidelines for treating adenocarcinomas and neuroendocrine neoplasms<sup>2</sup>. Uncertainty about the efficacy of available local and systemic treatment strategies complicates management. Even patients with limited local disease have relatively short life expectancy. In 2010, the World Health Organization (WHO) formally recognized this rare condition as a specific entity for colon cancer, aiming to better specify treatment options in the future<sup>3</sup>. MANECs represent 3% up to 9.6% of all colorectal cancers, and only 8 cases in the cecum have been reported to date, making the following case exceptionally rare<sup>4</sup>.

We present the case of a 60-year-old woman with acute abdominal symptoms who underwent surgery for acute appendicitis and was incidentally found to have a tumor in the cecum and ascending colon, later identified by pathology as MANEC.

## Case report

A 60-year-old woman with a history of type 2 diabetes mellitus and systemic arterial hypertension, with no surgical history, presented with acute colicky pain in the right hypochondrium, scoring 7/10 on the pain scale, radiating to the lower right quadrant, along with abdominal distension, nausea, and 3 episodes of vomiting with gastro-food content, without exacerbating or relieving factors. In the last 12 hours, the pain became sharp, scoring 10/10 on the pain scale, localized in the right iliac fossa. On physical examination, the patient was neurologically intact, cardiopulmonary system unremarkable, and abdomen distended due to adipose tissue, with increased peristalsis in intensity and frequency. Pain was present on palpation in the right hypochondrium and right iliac fossa; Murphy's sign was negative, McBurney's sign positive, with a palpable mass approximately 5 cm × 5 cm in the right iliac fossa, mobile, unattached to deep planes, and of firm consistency;



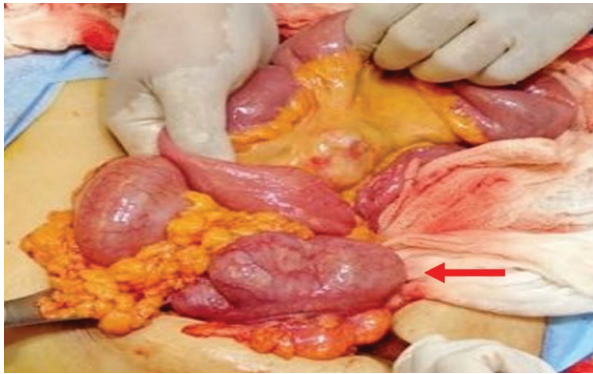
**Figure 1.** Simple-phase abdominal CT, axial view, showing an apparently cecum-dependent tumor (circle).



**Figure 2.** Simple-phase abdominal CT, transverse view, showing an apparently cecum dependent tumor (circle).

otherwise, findings were unremarkable. Lab test results: white blood cells  $12.67 \times 10^3/\mu\text{L}$ , hemoglobin 14.1 g/dL, hematocrit 44.2%, platelets  $367 \times 10^3/\text{mm}^3$ , neutrophils 82%, glucose 24.2 mg/dL, urea 32.4 mg/dL, BUN 15.0 mg/dL, creatinine 1.0 mg/dL, sodium 137.0 mmol/L, potassium 4.6 mmol/L, chloride 98.8 mmol/L, total bilirubin 0.18 mg/dL, direct bilirubin 0.44 mg/dL, indirect bilirubin 0.26 mg/dL, LDH 357 U/L, AST 15.5 U/L, ALT 10.5 U/L, alkaline phosphatase 107 U/L, CEA 2.13 ng/mL, CA-125 87.2 U/mL, and AFP 3.54 U/mL. Abdominal CT in simple phase revealed an image suggestive of complicated retrocecal acute appendicitis, with pronounced inflammatory changes and free fluid in the pelvic cavity, with nodular thickening of the cecal wall and multiple ileocecal and retroperitoneal lymph nodes (para-aortic, interaortic-caval, and retrocaval), the largest measuring 17 mm, possibly due to contiguous inflammatory process, though underlying colon lesions could not be ruled out (Figs. 1 and 2). Open surgical treatment was performed, revealing a tumor in the cecum and ascending





**Figure 3.** Tumor originating from the cecum obtained via exploratory laparotomy (arrow).



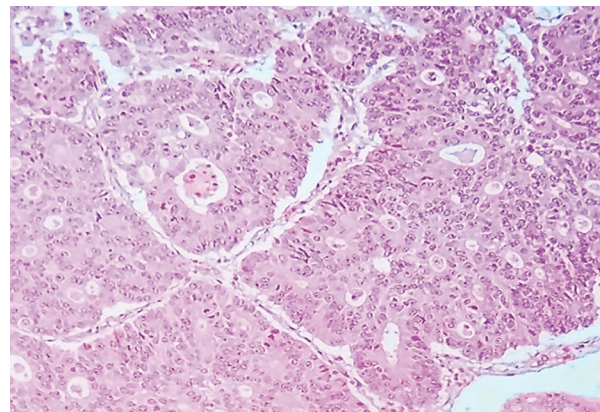
**Figure 4.** Surgical specimen obtained from right hemicolectomy and distal ileectomy.

colon, approximately 10 cm in size, of firm consistency, with inflammatory tissue and perforation in the mid-third, with fecal matter in the cavity, as well as an acute phase II process in the appendix. A right hemicolectomy and ileostomy were performed, and the specimen was sent for pathology. A half-inch laminar drain was placed towards the pelvic cavity, emerging in the lower right quadrant (Figs. 3 and 4).

Following surgery, the patient was sent to general surgery for 24-hour fasting, with functional ileostomy and a well-healed surgical wound. She received antibiotic therapy: metronidazole 500 mg IV every 8 hours for 14 days and ertapenem 1 g IV every 24 hours for 7 days. Oral intake was initiated and tolerated well, with output from the ileostomy. Pathology report: moderately differentiated adenocarcinoma with histological features of grade 2 moderately differentiated mixed adenoneuroendocrine carcinoma; acute, ulcerated, abscessed, transmural appendicitis in the postileal appendix (Figs. 5 and 6). Immunohistochemistry: intact MLH-1, intact MSH-6, positive CD56, positive synaptophysin, intact MSH-2,



**Figure 5.** Product of hemicolectomy and distal ileostomy, with postileal appendix (circle). A neoplastic lesion is visible in the ileum mucosa, ileocecal valve, and cecum.



**Figure 6.** Neoplastic proliferation with insular pattern, suggesting neuroendocrine differentiation.

intact PMS-2, and positive chromogranin. Postoperative treatment included analgesic therapy with celecoxib 100 mg orally every 12 hours for 14 days, diclofenac 100 mg orally every 12 hours for 7 days, and prokinetic therapy with cinitapride 1 mg orally every 8 hours for 30 days. The patient was referred to medical oncology, where she is currently under follow-up and being evaluated for chemotherapy initiation.

## Discussion

MANECs in the GI tract can appear in various organs, such as the esophagus, stomach, and colon, though

they are more common in the rectum<sup>5-7</sup>. Regardless of tumor location and stage, MANECs appear to be highly malignant tumors with a high risk of distant metastasis. Aggressiveness seems to depend on the endocrine component, regardless of its proportion<sup>2</sup>. Diagnosis is primarily based on the tumor cytology and architecture, confirmed through immunostaining with specific neuroendocrine markers, such as chromogranin, synaptophysin, and CD56 (for the neuroendocrine component), along with non-endocrine differentiation markers, such as keratin 7. It remains unclear whether MANEC is biologically closer to neuroendocrine tumors or adenocarcinomas; however, it is an extremely rare tumor, with most cases presented in isolated reports<sup>5</sup>. These tumors did not exhibit specific symptoms, nor did radiological or lab test results reveal unique findings; thus, diagnosis relies on postoperative histopathological and immunohistochemical studies<sup>8</sup>. Due to its rarity, little is known about the origin and best therapeutic options. Recent WHO recommendations suggest that MANEC should be treated as an adenocarcinoma; however, recent evidence suggests that treatment should be based on the more aggressive histological component<sup>9</sup>. MANECs require complex management, including patient-specific chemotherapy based on the tumor histology. The only therapeutic strategy for MANEC is complete surgical resection (R0 resection) of both primary tumors and metastases. Due to its aggressive nature and high recurrence rate, adjuvant chemotherapy is critical to treatment and significantly improves survival<sup>10</sup>. MANECs consist of 2 clearly distinct components (adenocarcinomatous and neuroendocrine) that respond differently to chemotherapy. As a result, selecting appropriate chemotherapy for both the primary tumor and distant metastases remains one of the most complex and challenging aspects of treating patients with MANEC<sup>11,12</sup>. In our case, the patient presented with nonspecific acute abdominal symptoms primarily related to an acute appendicular condition; however, physical examination revealed an apparently unrelated mass, and tomography identified a tumor originating from the colon, leading to surgical intervention. Histopathological analysis subsequently revealed the tumor type.

## Conclusions

Due to their rarity, significant debate continues around MANEC treatment. These tumors present no specific symptoms or radiological or laboratory findings, so diagnosis relies on postoperative histopathological and immunohistochemical studies. Due to the nonspecific symptoms,

highly aggressive nature, and metastatic potential of these tumors, physicians must remain aware of MANEC in their differential diagnoses. The literature on MANEC remains limited, primarily based on isolated case reports. Clear guidelines for diagnosis, surgical management, and follow-up criteria have yet to be established.

## Funding

None declared.

## Conflicts of interest

None declared.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

## References

1. Paredes MC, Velasco AA, Wong-Achi X. Carcinoma adenoneuroendocrino mixto de la ampolla de Vater: reporte de caso. *Rev Cir.* 2019;71:261-5.
2. Bosolino A, Ratto R. Tumores neuroendocrinos de colon y recto. *Acta Gastroenterol Latinoam.* 2019;48:327-37.
3. González González HH, Skrove JL, Sharma R, Sobrado J. A rare case of mixed adenoneuroendocrine carcinoma of the ileocecal valve. *Cureus.* 2019;11:e3942.
4. Gualdrini Ubaldo A. Cáncer colorrectal en la Argentina: organización, cobertura y calidad de las acciones de prevención y control. *Instituto Nacional del Cancer.* 2011;1:1-329.
5. Oneda E, Liserre B, Bianchi D, Rota LSavelli G, Zorzi F, et al. Diagnosis of mixed adenoneuroendocrine carcinoma (MANEC) after neoadjuvant chemotherapy for pancreatic and gastric adenocarcinoma: two case reports and a review of the literature. *Case Rep Oncol.* 2019;12:434-42.
6. Harada K, Sato Y, Ikeda H. Clinicopathologic study of mixed adenoneuroendocrine carcinomas of hepatobiliary organs. *Virchows Arch.* 2012;460:281-9.
7. Gurzu S, Kadar Z, Bara T, Bara T Jr, Tamasi A, Azamfirei L, et al. Mixed adenoneuroendocrine carcinoma of gastrointestinal tract: report of two cases. *World J Gastroenterol.* 2015;21:1329-33.
8. Düzköylü Y, Aras O, Bostancı EB, Keklik Temuçin T, Ulaş M. Mixed adeno-neuroendocrine carcinoma; case series of ten patients with review of the literature. *Balkan Med J.* 2018;35:263-7.
9. La Rosa S, Marando A, Sessa F, Capella C. Mixed adenoneuroendocrine carcinomas (MANECs) of the gastrointestinal tract: an update. *Cancers (Basel).* 2012;4:11-30.
10. Paspala A, Machairas N, Prodromidou A, Spartalis E, Ioannidis A, Kostakis ID, et al. Management of MANEC of the colon and rectum: a comprehensive review of the literature. *Mol Clin Oncol.* 2018;9:219-22.
11. Sato O, Tsuchikawa T, Yamada T, Sato D, Nakanishi Y, Asano T, et al. Metastatic mixed adenoneuroendocrine carcinoma of the liver successfully resected by hepatic trisectionectomy following chemotherapy: a case report. *Clin Case Rep.* 2019;7:491-6.
12. Nishida T, Blay JY, Hirota S, Kitagawa Y, Kang YK. The standard diagnosis, treatment, and follow-up of gastrointestinal stromal tumors based on guidelines. *Gastric Cancer.* 2016;19:3-14.

# Proximal jejunal GIST associated with massive gastrointestinal bleeding. Case report

*GIST en yeyuno proximal asociado a hemorragia masiva de tubo digestivo. Reporte de caso*

José J. Vargas-Montes<sup>1\*</sup>, Miguel E. Yado-López<sup>1</sup>, Pamela L. Huerta-Martínez<sup>1</sup>, Barbara I. Rojo-Rodríguez<sup>2</sup>, and Antonio Tirado-Moté<sup>3</sup>

<sup>1</sup>Departamento de Cirugía Digestiva y Endocrina, Centro Médico Nacional del Noreste, Unidad Médica de Alta Especialidad, Hospital de Especialidades No. 25, Instituto Mexicano del Seguro Social (IMSS), Monterrey, Nuevo León; <sup>2</sup>Departamento de Medicina Interna, Centro Médico Nacional del Bajío, IMSS, León, Guanajuato; <sup>3</sup>Departamento de Medicina Interna, Hospital General Regional Dr. Manuel Cárdenas de la Vega, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Culiacán, Sinaloa, Mexico

## Abstract

**Introduction:** Gastrointestinal stromal tumors (GIST) are rare, reported incidence is between 10 to 15 cases per million of habitants. They are usually located in the stomach (56%), small intestine (32%), colon-rectum (6%), and esophagus (<1%). Its symptoms include nausea, vomiting and abdominal fullness; 30% are asymptomatic. Incidental finding during abdominal surgery or imaging studies is common. Resection with negative margins is the standard treatment. **Case report:** A 69-year-old female patient who debuted with massive digestive tract bleeding, requiring surgical treatment. A tumor was detected at jejunum compatible with a GIST.

**Keywords:** Gastrointestinal Stromal Tumors. Jejunum. Small Intestine. Hemorrhage. Tumor.

## Resumen

**Introducción:** Los tumores del estroma gastrointestinal (GIST) son poco frecuentes, con una incidencia de 10 a 15 casos por millón de habitantes. Suelen localizarse en el estómago (56%), el intestino delgado (32%), el colon-recto (6%) y el esófago (< 1%). Sus síntomas incluyen náusea, vómito y plenitud abdominal; el 30% son asintomáticos. Es común su hallazgo incidental durante una cirugía abdominal o en estudios de imagen. La resección con márgenes negativos es el tratamiento estándar. **Caso clínico:** Mujer de 69 años que debuta con hemorragia masiva de tubo digestivo, requiriendo tratamiento quirúrgico. Se detecta un tumor de yeyuno compatible con GIST.

**Palabras clave:** Tumores del estroma gastrointestinal. Yeyuno. Intestino delgado. Hemorragia. Tumor.

### \*Correspondence:

José J. Vargas-Montes

E-mail: josevargasmontes.jv@gmail.com

Date of reception: 13-09-2022

Date of acceptance: 03-10-2022

DOI: 10.24875/CIRUE.M22000756

Cir Cir (Eng). 2024;92(5):665-668

Contents available at PubMed

www.cirugiaycirujanos.com

2444-0507/© 2022 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



## Introduction

Gastrointestinal stromal tumors (*GIST*, gastrointestinal stromal tumor) are rare tumors of the GI tract, originating from mesenchymal tissue<sup>1</sup>. Most studies report a clinical incidence of 10-15 cases per million people<sup>2</sup>.

GISTs are typically located in the stomach (56%), followed by the small intestine (32%), the colon-rectum (6%), and the esophagus (< 1%). Occasionally, they can affect the omentum, mesentery, and peritoneum. Initial symptoms may include nausea, vomiting, and abdominal fullness, although 30% of cases are asymptomatic; however, incidental detection of small, asymptomatic lesions during abdominal surgery or radiological and endoscopic studies is common<sup>1,2</sup>.

Immunohistochemical staining for the CD117 antigen is positive in 95% of GISTs and is considered a cornerstone for diagnosis<sup>3</sup>.

Resection with negative margins remains the standard treatment for GIST patients. The anatomical location of the tumor is a well-documented prognostic factor after radical surgery, with tumors in the small intestine having a worse prognosis than gastric tumors but a better prognosis than colorectal tumors, with extraintestinal locations being the least favorable<sup>4</sup>.

## Case report

A 69-year-old woman with a past medical history of total abdominal hysterectomy 35 years ago for uterine fibroids and left renal cyst resection 13 years ago, without apparent complications. She reports multiple red blood cell transfusions due to anemia of unknown origin. She has no other relevant history for her current condition.

She presented with a clinical course characterized by rectal bleeding without accompanying symptoms, prompting a diagnostic workup. Colonoscopy showed the rectum and sigmoid colon with abundant clots and 12 uncomplicated diverticula in the sigmoid colon; the rest of the study was unremarkable. At that time, she was diagnosed with lower GI bleeding due to self-limiting diverticular disease. However, she continued to have a clinical course characterized by multiple melena-like stools, requiring hospitalization under the gastroenterology service for a diagnostic and therapeutic workup. An intestinal transit study was performed, with no abnormalities, and antegrade enteroscopy revealed a 7 mm thickened mucosal

lesion in the proximal jejunum with color change and another raised, friable, ulcerated lesion, 20 mm in diameter, 10 cm distal to the former one. Biopsies were taken, with subsequent profuse arterial bleeding. A consultation was made with our service during the procedure, but no emergency surgical procedure was required due to cessation of bleeding following the placement of 2 hemoclips, with hospital observation. During her hospitalization, she had another episode of lower GI bleeding with copious bloody stools and signs of hypovolemic shock, along with a drop in hemoglobin down to 4.3 g/dL. Due to massive hemorrhage and signs of hemodynamic instability, treatment was initiated with red blood cell transfusion, and surgical treatment with exploratory laparotomy was performed, identifying a 4 cm × 2 cm hypervascularized tumor in the proximal jejunum, located 20 cm from the Treitz angle, non-perforated (Fig. 1), with no free fluid or other relevant findings. An intestinal resection of 10 cm was performed 10 cm from the Treitz angle, with mechanical side-to-side entero-enterostomy. The specimen was sent for definitive histopathological study. During surgery, red blood cell transfusion was administered, with a postoperative hemoglobin level of 8.4 g/dL.

After surgery, the patient was admitted to the hospital ward, dependent on vasoactive amines, with norepinephrine at a dose of 0.08 µg/kg/min, and was kept under observation in a joint management with gastroenterology and digestive surgery. With adequate clinical progression and an increase in hemoglobin to normal levels, she was discharged 8 days after surgery and scheduled for follow-up in the outpatient clinic.

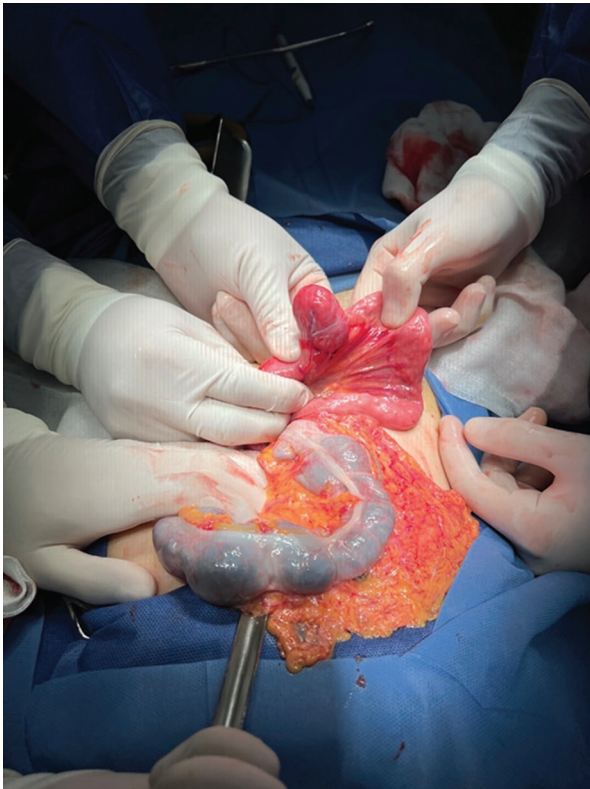
She returned to the outpatient digestive surgery clinic with a histopathology report concluding a low-grade 4 cm × 3 cm × 2.5 cm GI stromal tumor (*GIST*), with no necrosis and negative tumor margins, with < 5 mitoses in 50 high-power fields. Hematoxylin and eosin staining (Fig. 2) and immunohistochemistry were performed, with positive DOG1 and CD117 markers (Fig. 3); CKAE1/AE3, S100, and smooth muscle actin tested negative.

She was referred for oncology evaluation, with no need for adjuvant treatment due to the R0 tumor resection and absence of metastatic disease in extension studies, so she remains under medical monitorization.

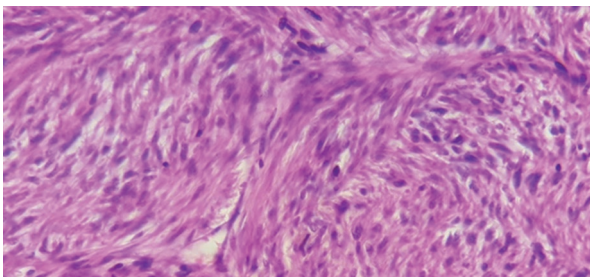
## Discussion

GISTs located in the jejunum are rare, representing 0.1% up to 3% of all GI tumors. Some cases present





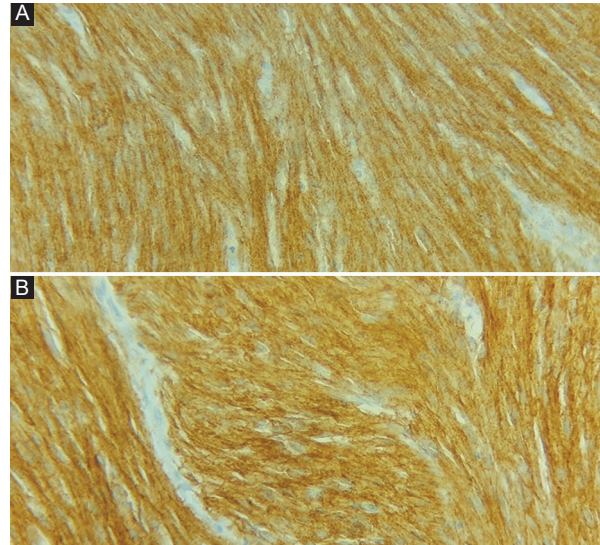
**Figure 1.** Jejunum GIST during exploratory laparotomy.



**Figure 2.** Hematoxylin-eosin staining at 40× magnification. Spindle-shaped neoplastic cells arranged in a syncytial pattern with elongated nuclei and eosinophilic cytoplasm.

with melena, hematemesis, and anemia due to recurrent bleeding. Acute GI bleeding is a common presentation in medical practice and may constitute a life-threatening emergency<sup>3,5</sup>.

GI bleeding has been reported in nearly 25% of jejunal GISTs; however, it is unusual for them to present with massive GI hemorrhages requiring emergency intervention<sup>5,6</sup>. In our case, the patient had massive bleeding, an uncommon presentation of this tumor, requiring emergency surgery during which a proximal jejunal tumor was detected.



**Figure 3.** Immunohistochemistry showing positivity for DOG1 (A) and CD117 (B).

Upper and lower endoscopy remains the first-line study for GI bleeding. Bleeding originating from the small intestine remains a diagnostic challenge due to the inaccessibility of this region with conventional endoscopy. Additional imaging modalities are necessary when upper and lower endoscopies are negative for bleeding data, including capsule endoscopy, coronary computed tomography angiography (CCTA), IV or oral contrast CT, enteroscopy, and magnetic resonance enterography<sup>3</sup>.

Microscopically, most GISTs show 3 main histologic subtypes: spindle cell type (the most common, 70%), epithelioid type (20%), and mixed type (10%). Immunohistochemistry is necessary for differentiation<sup>6,7</sup>.

GISTs are managed with various treatment modalities, including surgical resection, targeted medical therapies, chemotherapy, and radiotherapy; however, surgical resection is preferred due to the poor response of other modalities<sup>6</sup>. Surgical resection is the treatment of choice for any potentially resectable GIST > 2 cm, if the tumor is localized and symptomatic or if malignancy data are available on endoscopic ultrasound<sup>8</sup>. Postoperative surveillance alone is recommended if an R0 tumor resection (negative microscopic margins) is achieved<sup>1</sup>. In our case, complete surgical resection of the lesion was performed, with a histopathology report of spindle cell GIST with tumor-free margins, which was considered a successful treatment, and the patient was kept under surveillance only.

The prognosis for GISTs depends on tumor size, anatomical location, imaging findings, metastasis, and tumor rupture<sup>8</sup>. Numerous studies suggest that immunohistochemical expression is related to prognosis<sup>9</sup>. Fletcher's risk stratification is an established method for classifying the risk of recurrence<sup>10</sup>.

Tyrosine kinase inhibitors are useful in the treatment of GISTs as neoadjuvant preoperative therapy for 6 to 12 months for cytoreduction of large tumors to make them operable. If tyrosine kinase inhibitors are considered as part of the treatment plan, tumor mutation analysis is highly recommended. KIT gene mutations are found in approximately 80% of GISTs<sup>11-13</sup>.

## Conclusions

GISTs represent a low-incidence condition, especially those located in the jejunum and those presenting with massive GI bleeding. Due to their aggressive and nonspecific presentation, it is important to be knowledgeable about this type of tumor to establish an early diagnosis and provide timely treatment, as resection with clear margins improves patient survival.

## Acknowledgments

We wish to thank everyone involved in the publication of the article.

## Funding

None declared.

## Conflicts of interest

None declared.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that no patient data appear in this article.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

## References

1. Liu H, Santanello A, Jiménez M, Kumthekar N. Jejunal gastrointestinal stromal tumor (GIST) as a rare cause of GI bleed: a case report. *Cureus*. 2022;14:e24272.
2. Sánchez-Hidalgo JM, Durán-Martínez M, Molero-Payan R, Rufián-Peña S, Arjona-Sánchez A, Casado-Adam A, et al. Gastrointestinal stromal tumors: a multidisciplinary challenge. *World J Gastroenterol*. 2018;24:1925-41.
3. Mahmoud S, Salman H. Massive bleeding of a jejunal gastrointestinal stromal tumour: a rare case of a life-threatening presentation. *J Surg Case Rep*. 2020;2020:rja355.
4. Zhang Q, Shou CH, Yu JR, Yang WL, Liu XS, Yu H, et al. Prognostic characteristics of duodenal gastrointestinal stromal tumours. *Br J Surg*. 2015;102:959-64.
5. Mohamed AA, al Zahrani SM, Mohamed SA, Qureshi AS. Massive gastrointestinal haemorrhage unusual presentation of gastrointestinal stromal tumors of the jejunum: case report and literature review. *Cureus*. 2021;13:e14266.
6. Azimi B, Shahrabaf MA, Iranshahi M, Parsaeian F. A case of jejunal GIST revealed by hematemesis: unusual situation. *Int J Surg Case Rep*. 2022;94:107146.
7. Villafuerte Quimíz WL, Ostaiza Véliz IV, Williams Vargas LN, Palomeque Salazar X. Tumores del estroma gastrointestinal: revisión y manejo multidisciplinario. *J Am Health*. 2021;4:26-35.
8. Lim KT. Current surgical management of duodenal gastrointestinal stromal tumors. *World J Gastrointest Surg*. 2021;13:1166-79.
9. Qu H, Xu Z, Ren Y, Gong Z, Ju RH, Zhang F, et al. The analysis of prognostic factors of primary small intestinal gastrointestinal stromal tumors with R0 resection. *Medicine*. 2022;101:e29487.
10. Ito T, Kushida T, Sakurada M, Tanaka K, Sato K, Maekawa H. Complete wedge resection for duodenal gastrointestinal stromal tumour: a case series of three patients. *Int J Surg Case Rep*. 2022;90:106674.
11. El-Menyar A, Mekkodathil A, Al-Thani H. Diagnosis and management of gastrointestinal stromal tumors: an up-to-date literature review. *J Cancer Res Ther*. 2017;13:889-900.
12. Blay JY, Kang YK, Nishida T, Von Mehren M. Gastrointestinal stromal tumours. *Nat Rev Dis Primers*. 2021 Mar 18;7(1):22.
13. Serrano C, George S. Gastrointestinal stromal tumor: challenges and opportunities for a new decade. *Clin Cancer Res*. 2020;26:5078-85.

# Modified trident technique for surgical approach to facial lipoma

## *Técnica tridente modificada para el abordaje de un lipoma facial*

Nancy Trujillo-García<sup>1</sup>, Irma Y. Castillo-López<sup>2</sup>, Carmen A. Carrillo-López<sup>1</sup>, and Diana P. Mariscal-Arellano<sup>3\*</sup>

<sup>1</sup>Departamento de Cirugía Maxilofacial, Hospital General Regional 46, Instituto Mexicano del Seguro Social (IMSS); <sup>2</sup>Departamento de Otorrinolaringología y Cirugía de Cabeza y Cuello, Hospital General Regional 46, IMSS; <sup>3</sup>Departamento de Otorrinolaringología y Cirugía de Cabeza y Cuello, Centro Médico Nacional de Occidente, IMSS. Guadalajara, Jalisco, Mexico

### Abstract

**Introduction:** Lipomas are the most common tumors of mesenchymal origin throughout the body. Although they have low incidence in the oral cavity, their surgical approach can be challenging. **Case report:** 10-year-old male with a giant lipoma in the buccal and masticator space, an intraoral surgical approach was chosen using by modifying trident technique of Ramírez-Oropeza. **Discussion:** The main advantages and limitations of this intraoral approach are examined. **Conclusions:** An intraoral approach was selected because of less possibility of injuring the facial nerve, better esthetic results and less invasive, obtaining excellent results.

**Keywords:** Bichectomy. Lipoma. Masticator space. Intraoral approach.

### Resumen

**Introducción:** Los lipomas son los tumores de origen mesenquimatosos más comunes en todo el cuerpo. Aunque tienen una baja incidencia en la cavidad oral, su abordaje quirúrgico puede ser un enorme reto. **Caso clínico:** Varón de 10 años con un lipoma gigante del espacio geniano y masticador resecado mediante abordaje intraoral modificado de la técnica descrita por Ramírez-Oropeza. **Discusión:** Se describen las principales ventajas y limitaciones de un abordaje intraoral. **Conclusiones:** Se seleccionó este abordaje intraoral por la menor posibilidad de lesionar el nervio facial, los mejores resultados estéticos y ser menos invasivo, obteniendo excelentes resultados.

**Palabras clave:** Bichetomía. Lipoma. Espacio masticador. Abordaje intraoral.

#### \*Correspondence:

Diana P. Mariscal-Arellano

E-mail: prismariscal@hotmail.com

Date of reception: 08-05-2022

Date of acceptance: 09-07-2022

DOI: 10.24875/CIRUE.M22000757

Cir Cir (Eng). 2024;92(5):669-673

Contents available at PubMed

www.cirugiaycirujanos.com

2444-0507/© 2022 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Lipomas consist of mature adipocytes surrounded by a thin fibrous capsule<sup>1</sup> and typically develop superficially in subcutaneous tissue. They are soft, painless, and range in size from 1 cm to more than 10 cm. Malignant transformation into liposarcoma is rare<sup>2</sup>.

Although they are the most common mesenchymal tumors throughout the body, they are very rare in the oral cavity, with an incidence of 1% up to 4%<sup>3</sup>. In a study by Studart-Soares et al.<sup>4</sup> reviewing 450 intraoral lipomas, the most common sites were the buccal mucosa (38.7%), followed by the vestibule (7.8%), retromolar area (4.7%), and other locations (48.8%). No significant differences were found between men and women (52.2% were men, and 47.8% were women). Lipomas can appear at any age but are more commonly seen in individuals between the 4<sup>th</sup> and 6<sup>th</sup> decades of life<sup>5</sup>.

While the precise etiology remains unknown, primary theories suggest factors such as heredity, fat degeneration, hormonal changes, infection, accumulation of embryogenic lipoblastic cells at the site of origin, and chronic irritation<sup>6</sup>.

Diagnosis is primarily clinical, with imaging modalities aiding in differential diagnosis. Ultrasound can distinguish a lipoma from an epidermoid cyst or ganglionic cyst<sup>7</sup>, and MRI is highly specific for assessing extension and relationships with key anatomical structures. Differential diagnosis includes various conditions such as epidermoid cysts, hematomas, panniculitis, and other forms of adipocytic tumors<sup>7,8</sup>. If a lipoma presents symptoms, such as pain, restricted movement, or malignancy characteristics (e.g., rapid growth or changes during monitoring), a biopsy along with histopathology is recommended for definitive diagnosis<sup>2</sup>.

The primary treatment is surgery, with general risks including scar formation, seroma, and hematoma<sup>9</sup>. Alternative treatments include liposuction<sup>10</sup> and low-concentration deoxycholate injections, which were successfully used in a study of 6 patients<sup>11</sup>; however, further studies are required before recommending them systematically.

Various surgical approaches are available for tumors in the facial and neck regions. Medical criteria, based on the unique characteristics of each case, will determine the appropriate technique.

Several approaches for masticator space tumors have been described in the literature, including endoscopic surgery, extended submasseteric, transmandibular, transoral, and even combinations of these approaches in appropriate cases<sup>12-16</sup>.

Key aspects that should be considered in selecting an approach include tumor size, adjacent structure involvement, and tumor nature. In the case of a lipoma, the benign origin of the lesion means that a surgery that could cause major aesthetic or functional sequelae is not justified.

## Case Report

A 10-year-old boy with childhood obesity as the only relevant past medical history (weight/height ratio +5 standard deviations) came to our consultation with a left-sided mass in the masticator region, which had been slowly, progressively, and painlessly increasing in size over the past 7 months, without apparent involvement of adjacent structures.

Physical examination revealed the presence of acanthosis nigricans, gynecomastia, and a left masticator region tumor that was soft, well-demarcated, non-painful, mobile, not adherent to deep planes without any trophic changes to the skin (Fig. 1).

A simple CT scan of the head and neck showed asymmetry of the left hemiface due to soft tissue expansion. This mass was encapsulated, located immediately under the buccinator muscle, and had an attenuation of -99 HU, indicating fatty tissue density. Its limits included the depressor anguli oris muscle anteriorly, mandibular lower border inferiorly, the masseter muscle laterally, and extended superiorly to the zygomatic arch. It branched towards the infratemporal fossa, surrounding the lateral pterygoid muscle, with maximum dimensions of 53 mm × 44 mm × 46 mm (Fig. 2).

We opted for a modified intraoral approach using the trident technique<sup>1</sup>. Only buccopharyngeal chlorhexidine rinses were used as preoperative preparation. Following orotracheal intubation and balanced general anesthesia, Minnesota-type cheek retractors were placed for adequate exposure of the surgical site. Lidocaine with epinephrine was used for anesthesia and local vasoconstriction, providing hemostasis; a left high zygomatic block, left mandibular nerve block, and left C2 branch block were performed.

All techniques used 2% lidocaine with epinephrine in dental cartridges. The left high zygomatic block was achieved with a carpule syringe positioned obliquely from front to back and from below to above in the vestibular fold of the left upper second molar and maxillary tuberosity. For the left mandibular nerve block, a short needle was used at the left mandibular spix spine in an oblique anteroposterior direction.





**Figure 1.** Patient with a tumor located in the left masticator region.



**Figure 2.** Simple CT scan, coronal view, showing infratemporal extension of the lipoma.

Finally, for the masseter and C2 region, half a cartridge was used in the dental presentation in the vestibular fold towards the left mandibular angle, injected into the masseter muscle and the area of the homolateral mandibular angle.

Anatomic limits were then identified: the Stensen's duct papilla and the bite line on the cheek. A 1 cm incision was performed midway between these structures

using a No. 15 scalpel blade (Fig. 3); for better visualization, the incision was extended anteriorly to reach 4 cm in length, allowing access to the buccal and masticator spaces. Next, blunt dissection was performed until the buccinator muscle was visualized, continuing dissection through it, and separating the tumor from the left buccal, pterygoid, and infratemporal spaces (Fig. 4).

A complete lipomatous tumor was obtained (Fig. 5), fully encapsulated. Finally, simple sutures with 3-0 Vycril were used from deep layers, leaving a single surgical wound in the lateral wall of the oral vestibule (Fig. 6).

## Discussion

The masticator space is a virtual area divided into 3 subsections: masseteric, pterygomandibular, and temporal<sup>17</sup>. This space houses the masticatory muscles, blood vessels, and notably, the terminal branches of the zygomatic and buccal facial nerves<sup>18</sup>.

Various lesions may affect this space through contiguity, direct origin, or even as metastasis due to distant malignant tumors<sup>19-21</sup>. Of all body lipomatous tumors, around 13% occur in the head and neck, making them the most common benign tumors in this region<sup>22</sup>. However, they may adhere so firmly to adjacent structures that resection of portions of the masticatory muscles may be necessary for complete excision<sup>23</sup>.

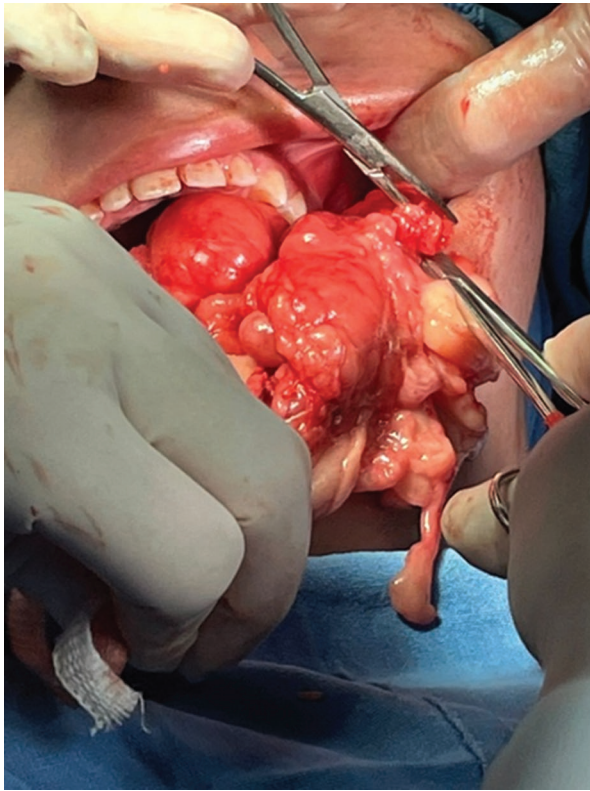
We propose an intraoral approach as an excellent option, offering rapid and efficient results with good functionality and aesthetic outcomes<sup>24</sup>.

During surgery, identifying and preserving Stensen's duct is crucial to reduce the risk of sialoceles or salivary fistulas. A sialocele is an inflammatory pseudocapsule containing salivary secretions within the soft tissues of the cheek, lacking proper drainage<sup>25</sup>. Post-operative monitoring is essential to detect complications. Botulinum toxin injections, compressive bandages, and percutaneous aspiration are first-line therapies for these complications<sup>26</sup>.

It should also be taken into account to adequately suture the flaps to avoid trauma, because the slow-growing mass creates a larger area of mucosa that, if not properly secured with the area of mucosa that, if not properly sutured, can fall off and become suture, can fall off and be injured during chewing<sup>27</sup>.

## Conclusions

The main limitation of the intraoral approach is the limited surgical field and potential contamination from



**Figure 3.** Blunt dissection reaching the buccinator muscle, allowing continued dissection through it.



**Figure 5.** Simple sutures with 4-0 Vycril.



**Figure 4.** Tumor completely extracted with its intact capsule.

Balancing the surgery safety and aesthetic considerations, we chose an intraoral approach. By extending the incision anteriorly up to 4 cm, we expanded the surgical field for improved visualization. Digital and blunt dissection with gauze helped detach the tumor, yielding a clean surgical field. This approach allowed for complete tumor resection with an intact capsule (Fig. 6) and optimal aesthetic results without complications.

Although the extraoral approach is widely used for masticator space tumors, if anatomical characteristics allow it, the intraoral approach is an excellent option that should always be considered. We recommend this approach whenever there is experience and assurance that the limited surgical field will adequately access the tumor location.

We conclude that in similar cases involving a well-demarcated, easily accessible tumor, the intraoral approach offers superior aesthetic results, preserves functionality, promotes faster and more efficient healing, and is a safe alternative<sup>29</sup>.

## Acknowledgments

The authors wish to thank the Otolaryngology Department of the Regional General Hospital 46 of the Mexican Social Security Institute.

oral microbiota, which often leads to preferring the extraoral approach<sup>28</sup>, though this approach risks facial nerve injury and leaves a visible scar.





**Figure 6.** Immediate postoperative image, showing facial symmetry.

## Funding

None declared.

## Conflicts of interest

None declared.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

## References

1. Brito-Vera JP, Gómez-Barajas LD, Santana-Montes DR, Ramírez Oropeza F. Bichetomía: técnica del tridente, presentación de una nueva técnica quirúrgica. *An Orl Mex.* 2020;65:37-42.

2. Goldstein A. Overview of benign lesions of the skin. En: Lee S, editor. UpToDate. Waltham, Mass., 2022. Disponible en: <https://www.uptodate.com>.
3. Alharbi AS. Intraoral lipoma of the cheek — a case report with a one-year follow-up and review of literature. *Cureus.* 2020;12:e10537.
4. Studart-Soares EC, Costa FW, Sousa FB, Negreiros-Nunes Alves, AP, Lima-Verde Osterne R. Oral lipomas in a Brazilian population: a 10-year study and analysis of 450 cases reported in the literature. *Med Oral Patol Oral Cir Bucal.* 2010;15:e691-6.
5. Taira Y, Yasukawa K, Yamamori I, Iino M. Oral lipoma extending superiorly from mandibular gingivobuccal fold to gingiva: a case report and analysis of 207 patients with oral lipoma in Japan. *Odontology.* 2012;100:104-8.
6. Furlong MA, Fanburg-Smith JC, Childers EL. Lipoma of the oral and maxillofacial region: site and subclassification of 125 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2004;98:441-50.
7. Rahmani G, McCarthy P, Bergin D. The diagnostic accuracy of ultrasonography for soft tissue lipomas: a systematic review. *Acta Radiol Open.* 2017;6:2058460117716704.
8. Berenguer B, Lorca-García C, Lancharro A, De Tomás E. Pediatric tumors of the buccal fat pad: lipoma and hemangioma. *Acta Chir Belg.* 2019;120:341-3.
9. Chandawarkar RY, Rodríguez P, Roussalis J, Tantri MD. Minimal-scar segmental extraction of lipomas: study of 122 consecutive procedures. *Dermatol Surg.* 2005;31:59.
10. Wilhelmi BJ, Blackwell SJ, Mancoll JS, Phillips LG. Another indication for liposuction: small facial lipomas. *Plast Reconstr Surg.* 1999;103:1864.
11. Rotunda AM, Ablon G, Kolodney MS. Lipomas treated with subcutaneous deoxycholate injections. *J Am Acad Dermatol.* 2005;53:973.
12. Iwai T, Sugiyama S, Hirota M, Mitsudo K. Endoscopically assisted intraoral resection of lipoma in the masticator space. *Ear Nose Throat J.* 2022;101:33-5.
13. Ferbeyre-Binelfa L. Abordaje submaseterino ampliado para la resección de lipoma del espacio masticatorio: nota anatomocirúrgica y reporte de un caso. *Gac Mex Oncol.* 2015;14:125-31.
14. Almeida-Parra F, Bueno -De Vicente A, Ranz-Colio A, Leyva-Moreno P, Núñez Paredes J, Picón Molina M, et al. Transmandibular approach in head and neck oncological surgery. *Chin J Dent Res.* 2020;23:257-64.
15. Lao WP, Han PS, Lee NH, Gilde JE, Inman JC. Transoral excision of parapharyngeal tumors. *Ear Nose Throat J.* 2021;100:NP454-8.
16. Noguchi T, Sugiura Y, Okada N, Tsuchiya Y, Hyasaka JI, Sasaguri KI, et al. A modified preauricular and transmandibular approach for surgical management of osteosarcoma of the mandibular condyle within the masticator space and infratemporal fossa: a case report. *J Med Case Rep.* 2019;13:58.
17. Chughtai S, Chughtai KA, Montoya S, Bhatt AA. Radiographic review of anatomy and pathology of the masticator space: what the emergency radiologist needs to know. *Emerg Radiol.* 2020;27:329-39.
18. Fernandes T, Lobo JC, Castro R, Oliveira MI, Som PM. Anatomy and pathology of the masticator space. *Insights Imaging.* 2013;4:605-16.
19. Baddour HM, Ochsner MC, Patel MR, Switchenko JM, Beitler JJ, Magliocco K, et al. Surgical resection is justifiable for oral T4b squamous cell cancers with masticator space invasion. *Laryngoscope.* 2021;131:E466-72.
20. Gordon JS, Mandel L. Masseteric intramuscular hemangioma: case report. *J Oral Maxillofac Surg.* 2014;72:2192-6.
21. Frade-Porto N, Delgado-Fernández J, García-Pallero MLA, Penas-Cuesta JR, Pulido Rivas P, Gil Simoes R. Subcutaneous tissue metastasis from glioblastoma multiforme: a case report and review of the literature. *Neurcirugia (Astur: Engl Ed).* 2019;30:149-54.
22. Morales-Cadena M, Acosta-Domínguez A, Hope-Guerreo JA. Lipoma del espacio parafaríngeo. *An ORL Mex.* 2007;52:3.
23. Tsumuraya G, Yamada H, Shimizu H, Hamada Y. Intramuscular lipoma in the masseter muscle: a case report. *Br J Oral Maxillofac Surg.* 2014;52:e21-3.
24. Coelho RCP, Oliveira EM, Silva GCC, Aguiar EG, Moreira AN, Souza LN. Intraoral excision of a huge cheek lipoma. *J Craniofac Surg.* 2018;29:e96-7.
25. Kalmar CL, Patel VA, Slonimsky G. Transoral floor of mouth lipoma resection: a technical multimedia analysis. *Am J Otolaryngol.* 2020;41:102572.
26. Aloua R, Slimani F. Salivary parotid cyst as an occurred complication of subangulomandibular approach of mandibular subcondylar fracture: a case report. *Ann Med Surg (Lond).* 2020;60:673-4.
27. De Sanctis CM. An unusual intraoral lipoma: a case report and literature review. *Am J Case Rep.* 2020;21:e923503-1-5.
28. Navaneetham A, Rao A, Gandhi A, Jeevan CA. Lipoma involving the masticator space. *Ann Maxillofac Surg.* 2011;1:93-4.
29. Tahim A, Ali S, Cheng L. An intra-oral approach to facial skin lumps — a move towards scarless surgery. *Oral Maxillofac Surg.* 2018;22:285-8.

# Vaccination during the COVID-19 pandemic: correspondence

## *Vacunación durante la pandemia de COVID-19: correspondencia*

Rujittika Mungmunpantipantip<sup>1\*</sup> and Viroj Wiwanitkit<sup>2</sup>

<sup>1</sup>Private Academic Consultant, Bangkok Thailand; <sup>2</sup>Department of Biological Science, Joseph Ayobabalola University, Ikeji-Arakeji, Nigeria

Dear Editor,

We would like to discuss the article entitled “Vacunación durante la pandemia de COVID-19: ¿cómo abordar la complejidad del fenómeno?” Caycho-Rodriguez and others The social sciences play a crucial role in ensuring vaccination success and providing accurate information on benefits, hazards, and supply. To enhance vaccination rates, strategies such as aggressive communication, eradicating disinformation, and establishing independent authorities to monitor and report on the process have been proposed<sup>1</sup>. The main issue at hand right now is still how widely people are accepting the COVID-19 vaccine. Regarding vaccination acceptance, the global public health sector continues to encounter substantial obstacles. One study found a connection between vaccine fear and mistrust of the local health-care system<sup>2</sup>. People may turn to public health solutions more or less frequently during a crisis, depending on how much faith they have in their local public health administration. How confident the public is in their local public health response will determine how well public health initiatives perform during the crisis. The public's faith in their local public health crisis response will have a significant impact on how successfully public health programs work during the COVID-19 pandemic<sup>3</sup>. Public trust in authorities, professionals, and scientists must strengthen to boost immunization rates and win over doubters. Studies, for instance, have connected anti-vaccine sentiments to a lack of trust in the local health-care system. Public trust in authorities, professionals, and scientists must strengthen to boost immunization rates and win over doubters. For instance,

studies have shown a connection between anti-vaccine beliefs and mistrust of the local health-care system<sup>2,3</sup>. How confident someone is in their ability to implement public health measures during a crisis will determine how prepared they are.

Editor, nos gustaría comentar un artículo titulado “Vacunación durante la pandemia de COVID-19: ¿cómo abordar la complejidad del fenómeno?” Caycho-Rodriguez y otros El valor de las ciencias sociales como clave para el éxito de la vacunación, la información adecuada sobre las ventajas, los riesgos y el suministro de vacunas, la comunicación asertiva, la erradicación de la desinformación y el establecimiento de organismos independientes para monitorear e informar sobre el proceso de vacunación pública son solo algunos de los métodos sugeridos para aumentar las tasas de vacunación<sup>1</sup>. El principal problema en este momento sigue siendo qué tan ampliamente acepta la gente la vacuna contra el COVID-19. En cuanto a la aceptación de la vacunación, el sector de la salud pública mundial sigue encontrando obstáculos importantes. Un estudio encontró una conexión entre el miedo a las vacunas y la desconfianza en el sistema de salud local<sup>2</sup>. Las personas pueden recurrir a soluciones de salud pública con mayor o menor frecuencia durante una crisis, según la confianza que tengan en la administración local de salud pública. La confianza del público en su respuesta local de salud pública determinará el desempeño de las iniciativas de salud pública durante la crisis. La fe del público en su respuesta local a la crisis de salud pública tendrá un impacto significativo en el éxito del

### \*Correspondence:

Rujittika Mungmunpantipantip  
E-mail: rujittika@gmail.com

Date of reception: 08-12-2022

Date of acceptance: 20-12-2022

DOI: 10.24875/CIRUE.M22000758

Cir Cir (Eng). 2024;92(5):674-675

Contents available at PubMed

www.cirugiaycirujanos.com

2444-0507/© 2022 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



funcionamiento de los programas de salud pública durante la pandemia de COVID-19<sup>3</sup>. La confianza pública en las autoridades, los profesionales y los científicos debe fortalecerse para aumentar las tasas de inmunización y ganarse a los escépticos. Los estudios, por ejemplo, han relacionado los sentimientos contra las vacunas con la falta de confianza en el sistema de salud local. La confianza pública en las autoridades, los profesionales y los científicos debe fortalecerse para aumentar las tasas de inmunización y ganarse a los escépticos. Por ejemplo, los estudios han demostrado una conexión entre las creencias antivacunas y la desconfianza en el sistema de salud local<sup>2,3</sup>. La confianza de alguien en su capacidad para implementar medidas de salud pública durante una crisis determinará qué tan preparado está.

## Funding

The authors declare that they have not received funding for this study.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Ethical disclosures

**Protection of humans and animals.** The authors declare that no experiments on humans or animals have been performed for this research.

**Confidentiality of data.** The authors declare that no patient data appear in this article.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

## References

1. Caycho-Rodríguez T, Gallegos M. Vacunación durante la pandemia de COVID-19: ¿cómo abordar la complejidad del fenómeno? *Cir Cir.* 2022;90:860-1.
2. Sookaromdee P, Wiwanitkit V. Factors influencing COVID-19 vaccine acceptance and hesitancy: correspondence. *Hum Vaccin Immunother.* 2022;18:2085471.
3. Mungmunpuntipantip R, Wiwanitkit V. COVID-19 vaccination hesitancy. *Recenti Prog Med.* 2021;112:596.

# Omicron's BQ.1.1 and XBB sub-variants: a global problem and management strategies

## Subvariantes BQ.1.1 y XBB de ómicron: un problema global y estrategias de manejo

Sergio A. Ramírez-García<sup>1</sup>, Diana García-Cruz<sup>2</sup>, and Carlos E. Cabrera-Pivara<sup>3,4\*</sup>

<sup>1</sup>Facultad de Ciencias Químicas, Universidad Autónoma Benito Juárez de Oaxaca, Oaxaca, Oax.; <sup>2</sup>Departamento de Consulta Externa, Servicios Médicos Particulares de Genética Médica, A.C, Guadalajara, Jal.; <sup>3</sup>Departamento de Salud Pública, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Jal.; <sup>4</sup>Dirección de Investigación, Centro Dermatológico Me Piel, Guadalajara, Jal. Mexico

To the Editor,

In response to the statement by the World Health Organization Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-VE) regarding the current "soup" variants, BQ.1.1 and XBB, and their health implications<sup>1-3</sup>, the published studies are limited but highlight 3 works mentioning that the BQ.1.1 variant is a descendant of the Omicron subvariant BA.5 and BQ.1. The BQ.1.1 variant has one of the highest numbers of immune-evasive mutations in regions coding for key antigenic sites of the Spike protein, including p.K444T, p.N460K, and p.R346T. This strain has a global rate of 65% (GISAID)<sup>1-3</sup>. The subvariant XBB\*, on the other hand, is a recombination of sublineages BA.2.10.1 and BA.2.75, with a global prevalence of 1.3%. It is a hybrid subvariant with seven key mutations enabling immune evasion<sup>1-3</sup>. Clinically, its distinctive characteristics have not been reported.

Considering this, and the importance of early clinical identification to reduce mortality, it can be achieved with an examination of the oral cavity, which has enabled differentiation among SARS-CoV-2 variants, even Omicron subvariants, each with unique features<sup>4</sup>. In light of new immune-evasive variants, trained immunity must be reactivated, for which we have the immunoregulator OM-85, which promotes phagocytosis and reduces viral expression, and has been foundational in Omicron management in the Sierra Sur of Oaxaca<sup>4</sup>. In the case of the XBB variant, we suggest calcium dobesilate, which blocks the binding of heparan sulfate to ACE2, or LP pirfenidone, which

downregulates ACE2<sup>5</sup>, thereby inhibiting SARS-CoV-2 entry into the cell. Currently, there are new viral receptors to consider, such as GPR78, exotoxins, and xylosyl transferases that, through docking, interact with SARS-CoV-2<sup>6</sup>. Carboplatin and gemcitabine are effective in such cases. Instead of viewing this as a global health issue, it is necessary to pursue innovative treatments, particularly those based on early diagnosis.

### Funding

None declared.

### Conflicts of interest

None declared.

### Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

### \*Correspondence:

Carlos E. Cabrera-Pivara

E-mail: carlos.pivara@academicos.udg.mx

2444-0507/© 2022 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Date of reception: 21-11-2022

Date of acceptance: 20-12-2022

DOI: 10.24875/CIRUE.M22000759

Cir Cir (Eng). 2024;92(5):676-677

Contents available at PubMed

[www.cirugiaycirujanos.com](http://www.cirugiaycirujanos.com)

## References

1. World Health Organization. TAG-VE statement on Omicron sublineages BQ.1.1 and XBB. (Consultado el 20-11-2022.) Disponible en: <https://www.who.int/news/item/27-10-2022-tag-ve-statement-on-omicron-sublineages-bq.1-and-xbb>.
2. Wong C. Subvariant 'soup' may drive wave. *New Sci.* 2022;256:11.
3. Callaway E. COVID 'variant soup' is making winter surges hard to predict. *Nature.* 2022;611:213-4.
4. Domínguez-Rodas J, López de la Mora DA, Dávalos NO, Ramírez-García SA, Rincón AR, Guzmán LR, et al. Detección clínica y descripción de las características socio-demográficas de la variante SARS-COV-2 omicron en población de la sierra sur de Oaxaca. *Cir Cir* 2022;90:567-472.
5. Seifirad S. Pifrenidone: a novel hypothetical treatment for COVID-19. *Med Hypotheses.* 2020;144:110005.
6. Achom A, Das R, Pakray P. An improved Fuzzy based GWO algorithm for predicting the potential host receptor of COVID-19 infection. *Comput Biol Med.* 2022;151:106050.

# Management guidelines in triplidemia due to respiratory viruses and the social importance of the clinical-genetic diagnosis algorithm of SARS-CoV2

*Estrategias de manejo en la triplidemia por virus respiratorios y la importancia social del algoritmo de diagnóstico clínico-genético de SARS-CoV2*

Sergio A. Ramírez-García<sup>1</sup>, Carlos E. Cabrera-Pivara<sup>2\*</sup>, José Domínguez-Rodas<sup>3</sup>,  
David A. López-de la Mora<sup>4</sup>, Sabina López-Toledo<sup>1</sup>, Felicitas Ortiz-García<sup>1</sup>,  
Reyna M. Hernández-Vásquez<sup>1</sup>, and Diego A. Cáceres-Gutiérrez<sup>4</sup>

<sup>1</sup>Instituto de Nutrición y Estudios Municipales, Universidad de la Sierra Sur, Miahuatlán de Porfirio Díaz, Oaxaca, Oax.; <sup>2</sup>Departamento de Salud Pública, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Jal.; <sup>3</sup>Unidad de Investigación de Medicina Traslacional y Medicina de Precisión, Servicios Médicos Profesionales, Particulares, A.C., Miahuatlán de Porfirio Díaz, Oaxaca, Oax.; <sup>4</sup>Departament de Ciències Biomèdiques, Centro Universitario Tonalá, Universidad de Guadalajara, Guadalajara, Jal. Mexico

To the Editor,

We revisit the recently published article by Ramírez-García<sup>1</sup>, which demonstrates how to detect different types of SARS-CoV-2 variants without molecular testing (Table 1) through examination of the oral cavity. From a social perspective, this is crucial because it enables a faster response to a global health issue like the “triple-demic” caused by the simultaneous infection with SARS-CoV-2 Omicron variant BQ.1.1, influenza virus H2N3, and respiratory syncytial virus (RSV). This approach facilitates differential diagnosis and the early initiation of treatment, potentially reducing mortality. In this context, one target is to strengthen trained immunity, for which the use of OM-85 may be reconsidered as it promotes the production of alpha-defensins that opsonize respiratory pathogens such as SARS-CoV-2, RSV, and influenza virus, among others<sup>2</sup>. Additionally, OM-85 has an antiviral effect vs SARS-CoV-2, reducing RNA from open reading frames and other genes. Other adjuvants worth reconsidering in addressing the triple-demic include extended-release pifrenidone, Vita Deyun®, and S-adenosylmethionine<sup>3,4</sup>, as they have

anti-inflammatory, antioxidant, and antiviral properties effective vs COVID-19. By silencing ACE2 expression, these agents prevent SARS-CoV-2 entry and simultaneously block the cytokine storm. S-adenosylmethionine, in particular, seems to have an effect on controlling mitochondrial oxidative stress during respiratory infections, especially in managing the accumulation of circulating mutated mitochondrial DNA, which has recently been reported in COVID-19<sup>5</sup>. Lastly, calcium dobesilate, which blocks the APOE-heparan sulfate system binding to ACE2 and prevents SARS-CoV-2 entry, should also be reconsidered; it is especially useful in Omicron variants that show significant genetic variability in the spike protein. In managing the triple-demic within both private and public hospital settings, it is essential to clinically identify the COVID-19 variant and initiate specific treatment within the first 2 to 4 days to reduce mortality and morbidity, along with specific antivirals for influenza and RSV. Therefore, it is proposed to consider as alternatives the viral fusion membrane inhibitors such as OM-85, calcium dobesilate, extended-release pifrenidone, and Vita

## \*Correspondence:

Carlos E. Cabrera-Pivara

E-mail: carlos.pivara@academicos.udg.mx

2444-0507/© 2022 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Date of reception: 18-11-2022

Date of acceptance: 04-12-2022

DOI: 10.24875/CIRUE.M22000760

Cir Cir (Eng). 2024;92(5):678-680

Contents available at PubMed

[www.cirurgiaycirujanos.com](http://www.cirurgiaycirujanos.com)



**Table 1. Clinical-Genetic Algorithm for Identifying SARS-CoV-2 Variants**

<b>SARS-CoV-2 Genetic Lineage or Variant</b>	<b>Oral Cavity Characteristics</b>	<b>Reason for Consultation</b>
Omicron (lineages BQ.1.1), known as "Hellhound"	Diffuse palatopharyngeal enanthem with petechiae, telangiectasia, increased blood vessels in the palate, exudative posterior palate and violet anterior palate	Maculopapular rash on the chest, back, and plantar area
Omicron (lineage BA.2.75, p.G446S and p.R493Q in the spike protein gene), known as "Centaur"	Erythematous palate with hyperproliferation of blood vessels	Peripheral neuropathy with moderate respiratory symptoms
Omicron (lineages BA.5, BA.4, BA.1)	Palatal vasculitis with ephelides, serpentine enanthem on the posterior palate	Proximal and distal peripheral neuropathy
Delta AY.4/Omicron BA.1 lineage (deltacron)	Palatopharyngeal vesicular enanthem in a cluster pattern, hyperproliferation of blood vessels and micro-ephelides, salmon-colored palate	Neuropathy, venous insufficiency, ocular and skin telangiectasia
Omicron (lineages BA.2.12 and BA.2.9)	Palate with exudative ulcerative oropharynx and petechiae	Macroangiopathy
Omicron (lineages BA.2 and BA.2.12.1)	Petechiae in the oropharynx accompanied by diffuse vesicular enanthem on the pharyngeal arch and base of the tongue	Mild flu-like symptoms
Omicron (lineages BA.2, BA.3, BA.4, and BA.5)	Violet posterior palate, diffuse palatopharyngeal vesicular enanthem, hyperproliferation of blood vessels	Peripheral neuropathy
Omicron (lineages B.1.1.529)	Single telangiectasia and vasculitis in the form of micro-ephelides, pale pink or salmon-colored anterior palate	Peripheral neuropathy
Omicron (lineages B.1.1.529)	Single telangiectasia and vasculitis in the form of micro-ephelides, pale pink or salmon-colored anterior palate	Peripheral neuropathy
Omicron (lineages B.1.1.529)	Single telangiectasia and vasculitis in the form of micro-ephelides, pale pink or salmon-colored anterior palate	Peripheral neuropathy
Omicron (lineages BA.1, BA.1.1)	Hyperproliferation of blood vessels, micro-ephelides, salmon-colored or pale pink palate	Peripheral neuropathy and diarrhea
Alpha lineage Q Beta lineage B.1.1351 Gamma (lineages P.1) Epsilon (B.1.43 and B.1.43)	Vesicular palatopharyngeal enanthem, posterior palate mucosa salmon or yellow in color, hypertrophy of gustatory corpuscles	Severe respiratory symptoms
Alpha (lineage B.1.1.7, GR clade)	Salmon or yellow-colored palatal mucosa, no enanthem	Severe respiratory symptoms
Delta (lineage B.1.617.2)	Palatopharyngeal vesicular enanthem in a racemose and diffuse pattern, palatal hematomas	Spontaneous epistaxis
Delta (lineages AY)	Palatopharyngeal enanthem in a racemose and/or diffuse pattern, exudative oropharynx with cracks	Spontaneous epistaxis
Mu (B.1.621, B.1.621.1)	Posterior pharynx with herpetiform vesicular enanthem and palatopharyngeal hematomas	Moderate respiratory symptoms
Prolonged COVID-19, Subacute COVID-19	Central palatal fibrosis, pale pink, light violet, or salmon-colored anterior and posterior palate	Peripheral neuropathy

Deyun®, as well as free radical antagonists like S-adenosylmethionine. In private health care settings in Mexico, medications are available to tackle the tripledemic, making it a proposal for public policy consideration.

## Acknowledgments

The authors wish to thank the CB-Xpert Clinical Pathology Laboratory, Miahuatlán de Porfirio Díaz, Oaxaca.

## Funding

None declared.

## Conflicts of interest

None declared.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

## References

1. Ramírez-García SA. Palato-pharyngeal enanthem in the genetic variants of the COVID-19 and its sensitivity. *Cir Cir.* 2022;90:429-30.
2. Domínguez-Rodas J, Ramírez-García SA, Rincón-Sánchez AR, Dávalos-Rodríguez NO, Juárez-Pérez MH, Cabrera-Pivaral CE. COVID-19 pandemic experience of the management of outpatient rural population from the Sierra Sur de Oaxaca, Mexico. *Cir Cir.* 2022;90:133-4.
3. Cabrera Pivaral CE, Rincón Sánchez AR, Dávalos Rodríguez NO, Ramírez García SA. Parsonage Turner syndrome associated with COVID-19: about two family cases. *Neurologia.* 2022 Feb 3. Online ahead of print.
4. Aguilar-Lemarroy A, López-Urbe A, Sánchez-Corona J, Jave-Suárez LF. Severe acute respiratory syndrome coronavirus 2 ORF3a induces the expression of ACE2 in oral and pulmonary epithelial cells and the food supplement Vita Deyun® diminishes this effect. *Exp Ther Med.* 2021;21:485.
5. Scozzi D, Cano M, Ma L, Zhou D, Zhu JH, O'Halloran JA, et al. Circulating mitochondrial DNA is an early indicator of severe illness and mortality from COVID-19. *JCI Insight.* 2021;6:e143299.